DOI 10.1007/s10593-021-02916-4
Chemistry of Heterocyclic Compounds **2021**, *57*(4), 383–409

Pyrimido[1,2-*a*]benzimidazoles: synthesis and perspective of their pharmacological use

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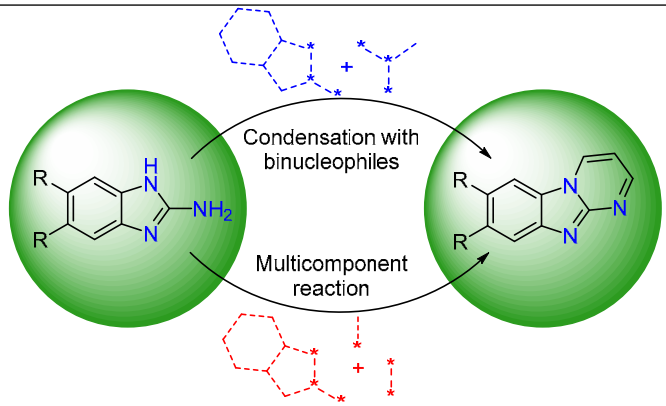
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2021, *57*(4), 383–409

Submitted November 13, 2020
Accepted after revision January 12, 2021



The review presents data on the synthesis as well as studies of biological activity of new derivatives of pyrimido[1,2-*a*]benzimidazoles published over the last decade. The bibliography of the review includes 136 sources.

Keywords: 2-aminobenzimidazole, pyrimido[1,2-*a*]benzimidazoles, polynitrogen-containing heteroarenes, heterocyclization, multicomponent reactions.

Nitrogen-containing heterocyclic compounds are the basis of many natural and synthetic biologically active substances.[1] More than two-thirds of the known drugs used in clinical practice contain heterocyclic and, above all, nitrogen-containing fragments within their structure. Over the past decades, the chemistry of aza-heterocycles has received considerable attention due to the wide spectrum of their biological activity and numerous therapeutic applications in medicine.

Of nitrogenous heterocycles, azoloazines containing fragments similar to the natural heterocycles purines and pyrimidines are currently of great practical importance. Thus, non-natural nucleosides abacavir, famciclovir, remdesivir are known, which are the products of structural modifications of all the components of the nucleotide exhibiting excellent indicators of antiviral action (Fig. 1).[2–4]

In addition to the generally accepted nucleoside forms, the azoloazines themselves are relevant in the search for means of combating diseases on a global scale. Nitroazolo-

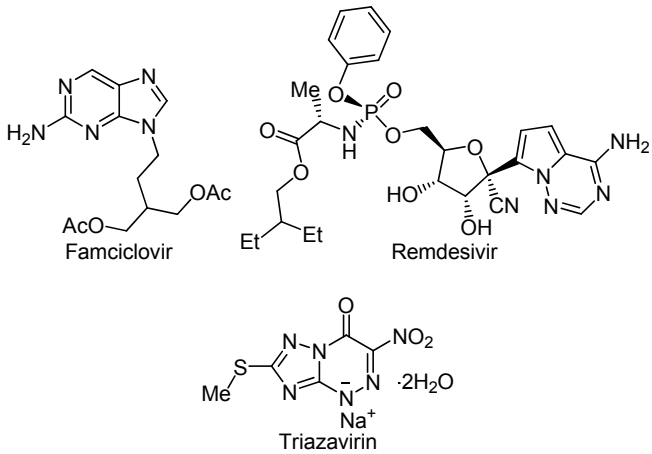


Figure 1. Azoloazine-based antiviral drugs.

[5,1-*c*][1,2,4]triazines and nitroazolo[1,5-*a*]pyrimidines, a new family of antiviral compounds has been found.[5] The

medication Triazavirin (2-methylsulfanyl-6-nitro[1,2,4]-triazolo[5,1-*c*][1,2,4]triazin-7-one sodium salt dihydrate) showed a broad spectrum of antiviral action and high efficacy. The medication protects against infection caused by influenza viruses,[6–9] ARVI,[10] tick-borne encephalitis.[11,12] Triazavirin has been shown to be effective in treating patients with moderate COVID-19.[13,14] Antiviral medication 5-methyl-6-nitro-7-oxo-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine L-arginine salt monohydrate is at the stage of clinical trials.[15,16]

At the same time, this is not the only method of constructing the important heterocyclic structures with relevant biological activity. Thus, numerous compounds containing benzimidazole scaffold which are isosteres of the nitrogenous bases of nucleic acids are known.[17] Some of the most important drugs containing the benzimidazole structural element are shown in Figure 2.

Currently, numerous compounds containing the benzimidazole moiety are known to exhibit various types of biological activity, including analgesic,[18] antibacterial,[19] anticancer,[20,21] antifungal,[22] antiHIV,[23] anti-inflammatory,[24] antimalarial,[25] antimicrobial,[26] antioxidant activity,[27] as well as anti-tuberculosis[28] and varied antiviral activities.[29] Thus, the creation of pharmacologically sound benzimidazole derivatives is an important task that requires complex synthetic approaches.

Among the methods for the structural modification of benzimidazole scaffolds, the approach consisting in the creation of polycyclic condensed analogs with the participation of five- and six-membered structures is of particular interest and independent significance. Of the large number of polycyclic derivatives of benzimidazoles, pyrimido[1,2-*a*]benzimidazoles are of significant interest, having structural similarity both with benzimidazoles and with various azolo[1,5-*a*]pyrimidines which have also proven themselves as structures with relevant biological properties, including antiviral,[5] antibacterial,[30] antiseptic,[31,32] anticancer,[33] and anti-glycation[34] effects. In addition, annulated benzimidazoles with a conjugated planar structure exhibit relevant photophysical properties and find application in optoelectronics as phosphors and fluorescent dyes in textile and polymer materials.[35] Besides, pyrimido[1,2-*a*]benzimidazoles are of interest from the aspect of further modifications in the creation of macrocyclic derivatives, including, in particular, purinobenzimidazoles which are not described in the literature.

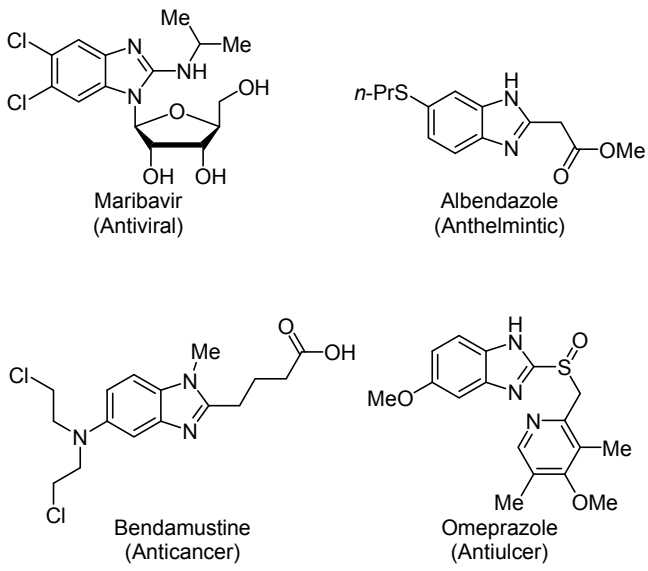


Figure 2. The drugs based on benzimidazole.

This review examines and discusses the data on the main methods of construction and the possibilities of practical application of pyrimido[1,2-*a*]benzimidazole derivatives published in the past 10 years. The increased interest in such heterocyclic systems is due to the promise of the emergence of unique properties (biological active, photophysical, structural, etc.) because of the practical significance of the benzimidazole and azolo[1,5-*a*]-pyrimidine scaffolds contained in pyrimido[1,2-*a*]-benzimidazoles.

To obtain the target heterocyclic systems of this type, two main synthetic strategies are currently actively used: the reaction of aminobenzimidazoles with bifunctional synthetic equivalents, and the construction of a pyrimidobenzimidazole structure by the method of multicomponent reactions.

The reaction of aminobenzimidazoles with bifunctional synthetic equivalents

One of the approaches to the construction of pyrimido-[1,2-*a*]benzimidazoles and related polycyclic derivatives is based on the annulation of substituted benzimidazoles with bifunctional synthetic equivalents, the nature of which determines the reaction conditions. The most common and widely used example of bifunctional synthetic equivalents are derivatives of unsaturated carbonyl compounds.

A team of authors from Egypt described the synthesis of pyrimidobenzimidazole derivative **3** containing a pyrazole substituent at position 2 (Scheme 1). It was demonstrated that the reaction of 2-aminobenzimidazole (**1a**) with the unsaturated ketone derivative **2** in EtOH under the conditions of basic catalysis leads to the target compound in good yield (71%).[36] Another close illustration of the reaction of 2-aminobenzimidazoles with α,β-unsaturated carbonyl compounds **4** is the preparation of pyrimido[1,2-*a*]-benzimidazoles **5a**–**t** using a highly active reusable catalyst based on heterogeneous layered double hydroxides on a polyacrylic support (PAA-g-LDH) (Scheme 1, Table 1).[37] Carrying out the reaction without a solvent made it possible to obtain the final products **5a**–**t** in more than 85% yields.

Later publications report reactions with ethyl 3-cinnamoyl-5-methyl-1-phenyl-1*H*-pyrazoles **6a**,**b** and **8a**–**d** in EtOH with AcOH as a catalyst.[38,39] However, in contrast to the above approach, in these reactions, a pyrazole substituent is introduced at position 4 of the benzimidazo[1,2-*a*]pyrimidine system with the formation of products **7a**,**b** and **9a**–**d** (Scheme 1).

Photochemical condensation of 2-aminobenzimidazole (**1a**) and 2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-

Scheme 1

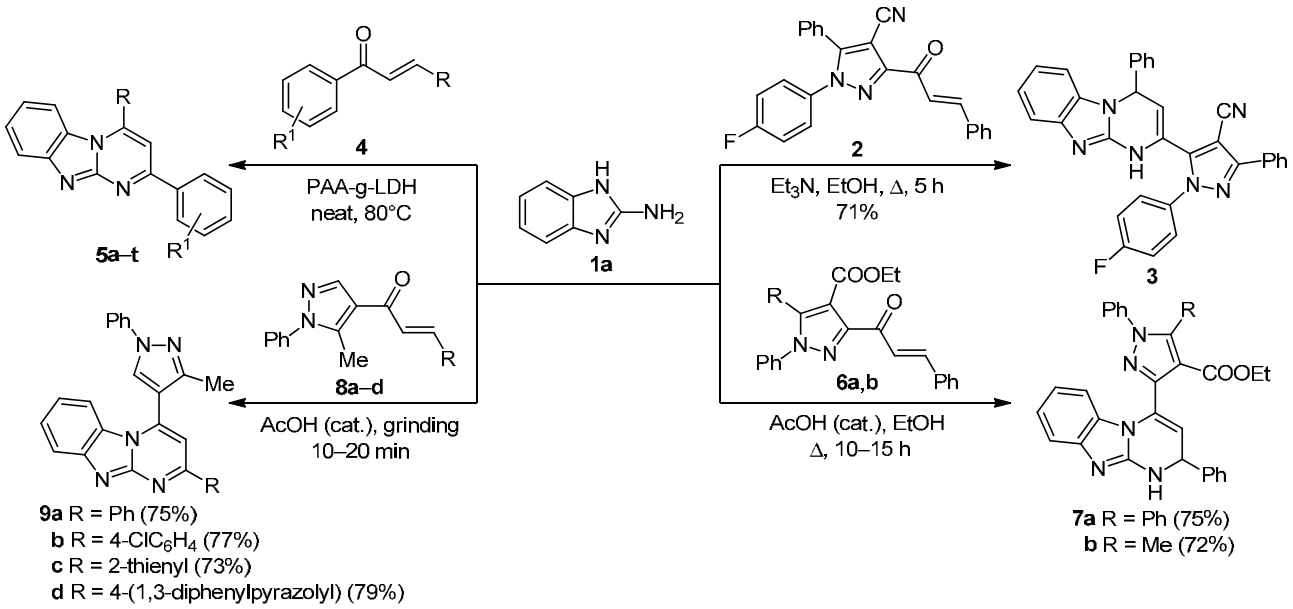
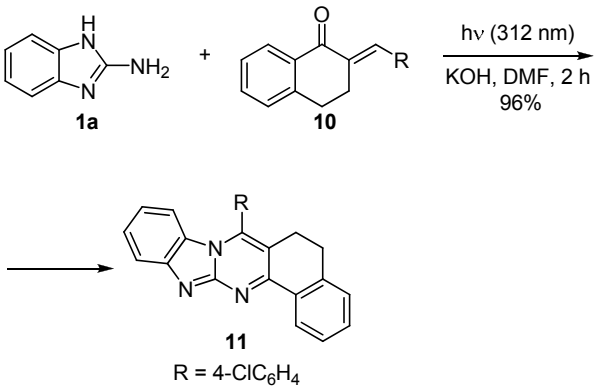


Table 1. The yields of pyrimido[1,2-*a*]benzimidazoles **5a**–**t**

Compound	R	R^1	Reaction time, min	Yield, %
5a	4-*i*-PrC_6H_4	H	20	92
5b	3-$MeOC_6H_4$	H	22	89
5c	4-ClC_6H_4	H	22	90
5d	4-MeC_6H_4	H	28	91
5e	4-FC_6H_4	H	24	90
5f	3,4,5-$(MeO)_3C_6H_2$	H	29	91
5g	4-$EtOC_6H_4$	H	20	92
5h	3-$O_2NC_6H_4$	H	25	85
5i	3-BrC_6H_4	H	29	89
5j	3-MeC_6H_4	3-OMe	28	91
5k	2-MeC_6H_4	3-Me	24	91
5l	3-FC_6H_4	4-Me	28	89
5m	4-MeC_6H_4	4-Me	23	90
5n	2-FC_6H_4	4-Br	29	91
5o	4-*i*-PrC_6H_4	4-Me	22	92
5p	3,4,5-$(MeO)_3C_6H_2$	4-Me	25	89
5q	4-BrC_6H_4	4-Me	29	88
5r	2-ClC_6H_4	4-F	26	87
5s	4-FC_6H_4	4-F	25	89
5t	3-MeC_6H_4	4-Br	27	87

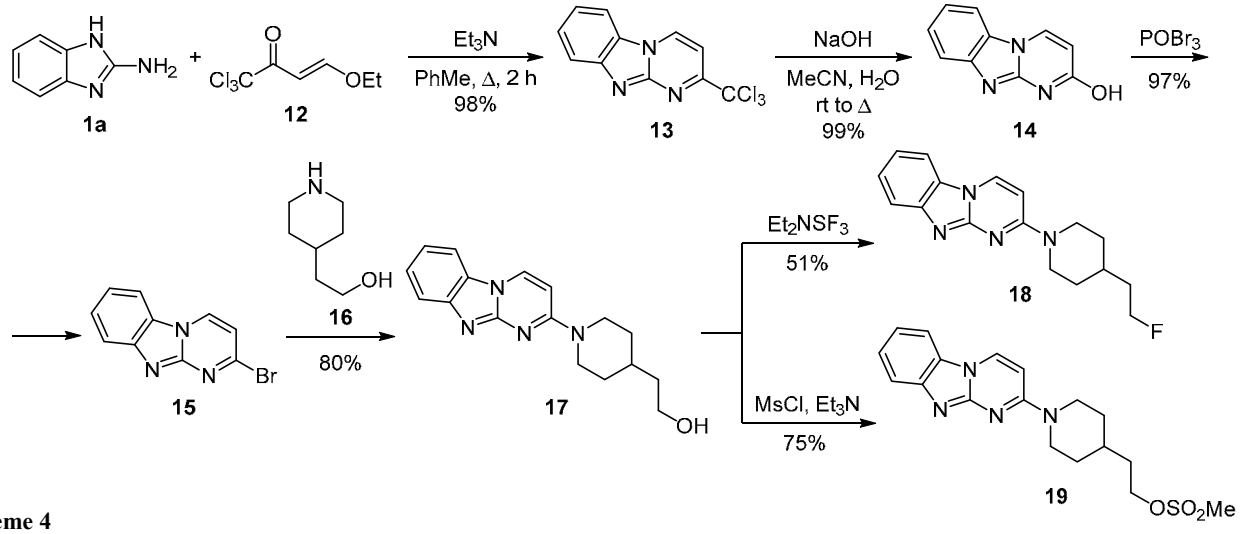
1(2*H*)-one (**10**) in the presence of KOH and DMF[40] is demonstrated in Scheme 2. It was found that 312 nm is the most suitable wavelength for the reaction within 2 h resulting in 96% yield of product **11**. These examples indicate the importance of selection of conditions in the construction of the pyrimidobenzimidazole molecular structure.

Scheme 2

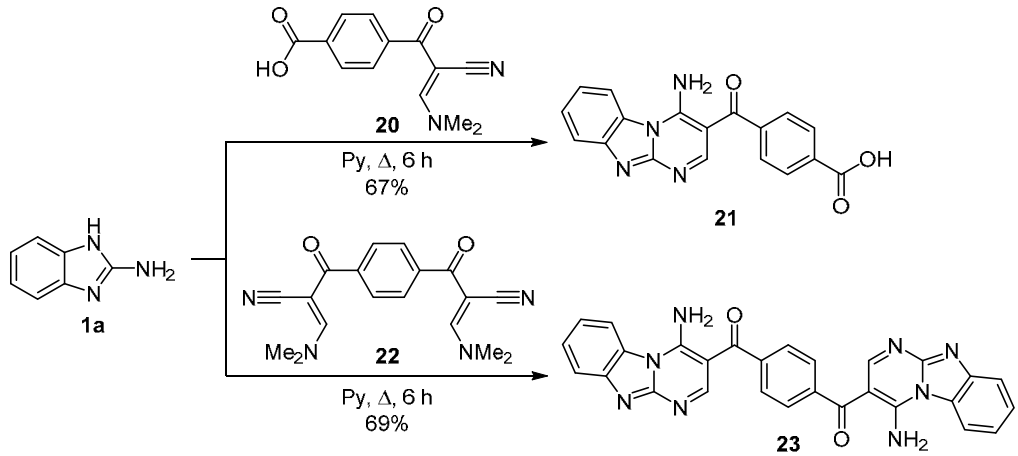


In 2014, Gao et al. developed an approach to the synthesis of the tracer for positron emission tomography T808 (**18**) and the corresponding mesylate precursor T808P (**19**) which are necessary for the detection of Alzheimer's disease (Scheme 3). The developed method included interaction of 2-aminobenzimidazole (**1a**) with 4-ethoxybutan-2-one (**12**). Subsequent hydrolysis of the trichloromethyl group in compound **13** leads to the formation of 2-hydroxypyrimido[1,2-*a*]benzimidazole (**14**), bromodeoxygenation of which and further nucleophilic substitution with 2-(piperidin-4 yl)ethanol (**16**) leads to the formation of adduct **17**. Treatment of the latter with *N*,*N*-diethyltrifluorosulfamine and methanesulfonyl chloride leads to reference standard **18** in 51% yield and mesylate **19** in 75% yield. A number of patent studies are devoted to the synthesis and elucidation of the properties of derivatives of compound **15** in relation to neurodegenerative diseases.[42–44]

Scheme 3



Scheme 4

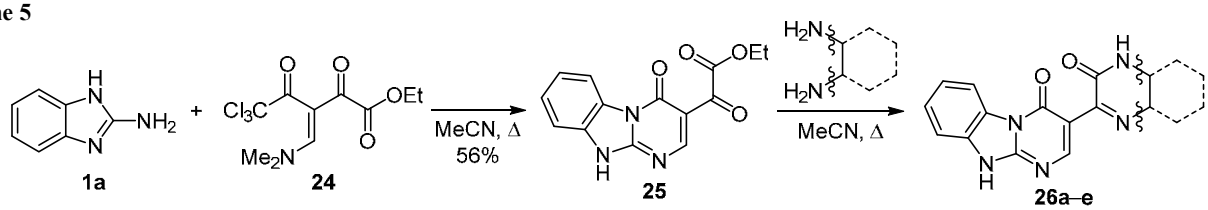


β-Enamine derivatives of ketones are important representatives of unsaturated carbonyl compounds for the construction of the pyrimidobenzimidazole system. Egyptian authors report the use of enaminonitriles **20** and **22** in regioselective synthesis of pyrimidobenzimidazole derivatives **21**, **23**. The use of pyridine as a solvent allows the target products to be obtained in good yields (Scheme 4).[45]

Brazilian scientists described the cyclocondensation reaction of β-enamino diketone **24** and 2-aminobenzimidazole (**1a**) resulting in the formation of a glyoxylic derivative of pyrimido[1,2-*a*]benzimidazole **25**.[46] The reaction is characterized by a good yield of the product. The obtained glyoxylate **25** is converted into pyrazinones and quinoxalinones **26a**–**e** by the action of a number of 1,2-diamines (Scheme 5).

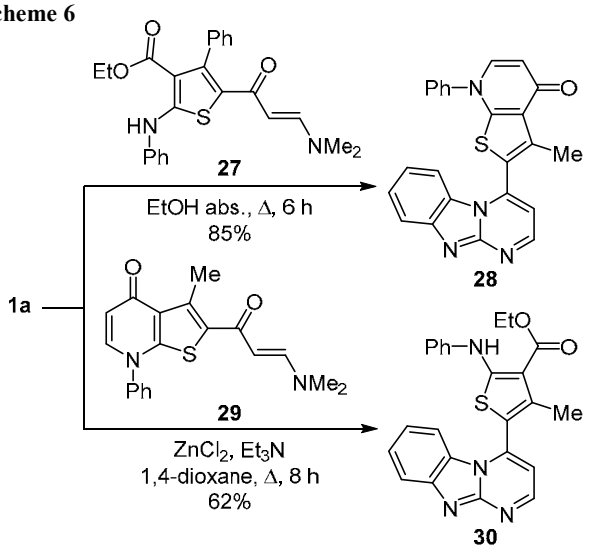
Also presented are the results on the preparation of pyrimido[1,2-*a*]benzimidazoles **28**, **30** containing thiophene and thieno[2,3-*b*]pyridinone fragments employing enaminones **27**, **29** (Scheme 6).[47,48] Interest in thiophene-containing derivatives is justified by the wide

Scheme 5



	26a	26b	26c	26d	26e
		1 : 1			1 : 1
Yield, %	78	89	91	52	56

Scheme 6

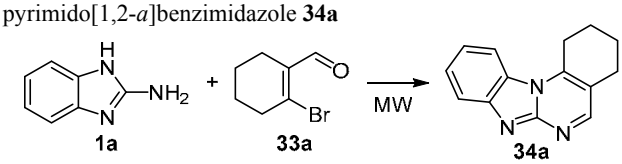


representation of this important structural fragment in biologically active compounds such as vitamin H, xanthopappin A, etc.

Another variation of the reaction of compound **1a** with β-enamines was demonstrated by Egyptian scientists using pyridazine derivative **31** as an example. The process takes place upon heating under reflux in pyridine to form pyrimidobenzimidazole **32** containing the pyridazine fragment which is relevant in medicinal chemistry (drugs hydralazine, dihydralazine) (Scheme 7).[49] The approaches presented in this work using enamino ketones indicate the great potential of these reagents as building blocks in the creation of pyrimidobenzimidazole scaffold.

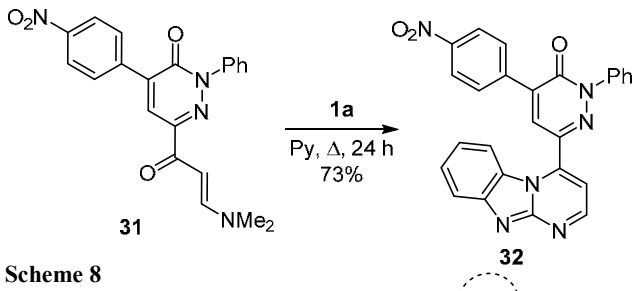
The use of α,β-unsaturated aldehydes to construct the pyrimidobenzimidazole scaffold was illustrated by Cho et al. The research team showed that β-bromo-α,β-unsaturated aldehydes **33a–j** react with 2-aminobenzimidazole (**1a**) to form pyrimido[1,2-*a*]benzimidazoles **34a–j** (Scheme 8).[50] Optimization of the synthesis conditions (Table 2) showed

Table 2. Optimization of conditions for the synthesis of pyrimido[1,2-*a*]benzimidazole **34a**

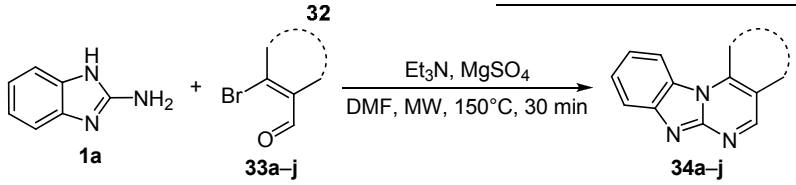


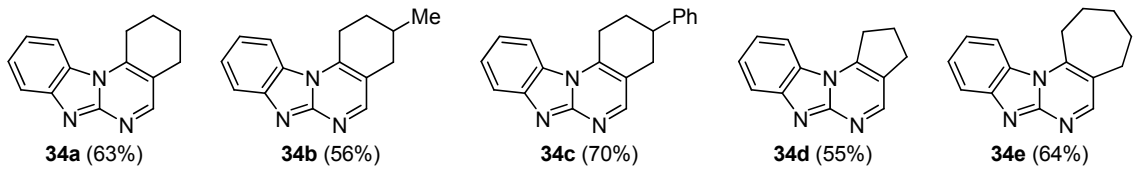
Entry	Base	Additive	Solvent	Yield, %
1	K_2CO_3		DMF	42
2	–		DMF	8
3	K_2CO_3		DMF	45
4	Cs_2CO_3		DMF	28
5	NaO*t*-Bu		DMF	31
6	K_3PO_4		DMF	37
7	Et_3N		DMF	50
8	**Et_3N**	**$MgSO_4$**	**DMF**	**63**
9	Et_3N	MS 4 Å	DMF	49
10	–	$MgSO_4$	DMF	30
11	Et_3N	$MgSO_4$	DMSO	43
12	Et_3N	$MgSO_4$	1,4-Dioxane	0
13	Et_3N	$MgSO_4$	DMF	62
14	Et_3N	$MgSO_4$	DMF	43

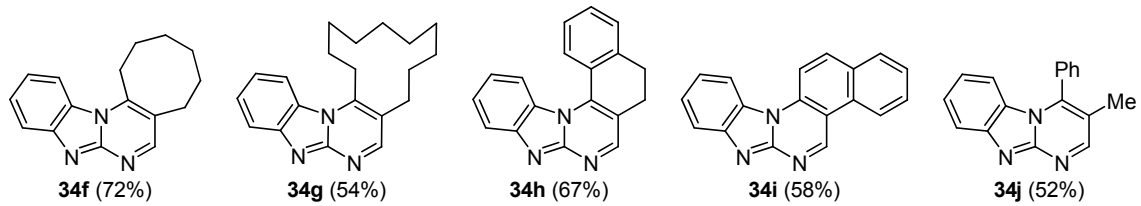
Scheme 7



Scheme 8





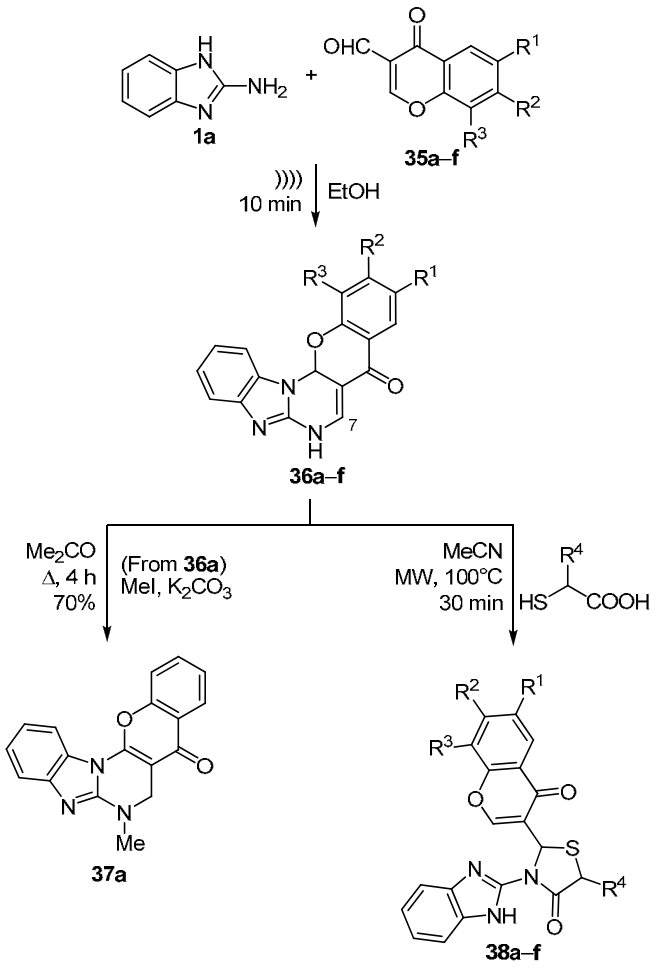


that the use of DMF as a solvent under microwave irradiation in the presence of Et_3N and $MgSO_4$ is optimal. The developed approach represents a novel and efficient method for the synthesis of the hybrid structure of pyrimidobenzimidazoles from readily available β-bromo-α,β-unsaturated aldehydes.

Chromene aldehydes **35a**–**f** were also successfully used in the synthesis of a number of condensed pentacyclic chromeno[3',2':5,6]pyrimido[1,2-*a*]benzimidazoles **36a**–**f** (Scheme 9).[51] According to the authors of the publication, the reaction was carried out under the conditions of sonochemical activation which resulted in product high yields (up to 88%) and also made it possible to significantly reduce the reaction time to 10 min. Due to the limited solubility of compounds **36a**–**f**, for unambiguous determination of the structure by NMR, the methylation of compound **36a** was carried out with the formation of *N*-methyl derivative **37a** the structure of which was established on the basis of 2D NMR spectra. In addition, the reaction of derivatives **36a**–**f** with thiocarboxylic acids was investigated and a mechanism for the formation of the products **38a**–**f** was proposed. The author's interpretation of the formation of thiazolinones **38** involves the reaction of thioglycolate with the C-7 atom and the subsequent opening of the pyrimidine fragment. A significant advantage of the described approach is that in all reactions the chromone fragment of the molecule remains intact since the opening of the pyran ring is a limiting factor in many reactions with the participation of chromones.

The instability of the chromone fragment is convincingly presented in a publication from 2016. Thus, the reaction of chromonecarbonitrile **39** with 2-aminobenzimidazole (**1a**) proceeds *via* the γ-opening of the pyrone ring followed by cycloaddition to the nitrile group and the formation of the pyrimidobenzimidazole structure **40**. Condensation was successfully carried out by heating in EtOH under reflux for 30 min with a product yield of 74% (Scheme 10).[52]

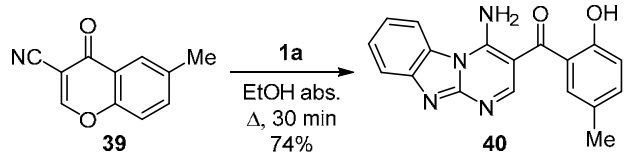
Scheme 9



	R^1	R^2	R^3	Yield, %
36a	H	H	H	88
36b	Me	H	H	80
36c	*i*-Pr	H	H	82
36d	Cl	H	H	80
36e	Cl	Me	H	68
36f	Br	H	Br	68

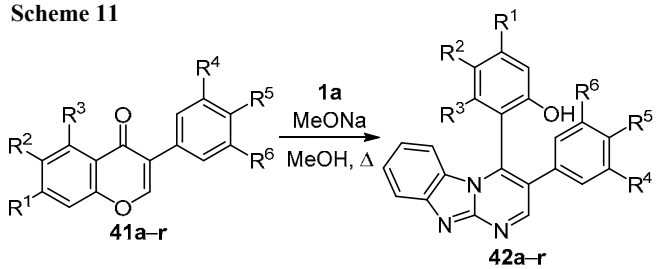
	R^1	R^2	R^3	R^4	Yield, %
38a	H	H	H	H	79
38b	Me	H	H	H	62
38c	Cl	H	H	H	45
38d	Cl	Me	H	H	48
38e	H	H	H	Me	58
38f	Cl	H	H	Me	39

Scheme 10



In addition, a method was developed for the construction of condensed derivatives of pyrimido[1,2-*a*]benzimidazoles **42a**–**r** by cyclocondensation of 2-aminobenzimidazole (**1a**) with isoflavones **41a**–**r** in MeOH in the presence of 3 equiv of MeONa (Scheme 11).[53] This process is also accompanied by opening of the pyran ring followed by

Scheme 11

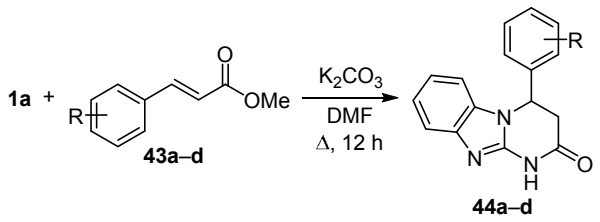


	R^1	R^2	R^3	R^4	R^5	R^6	Yield, %
42a	O*i*-Pr	H	H	H	H	H	88
42b	OH	H	H	H	H	H	74
42c	OMe	H	H	H	H	H	89
42d	OH	H	H	H	OH	H	71
42e	OMe	H	H	H	OMe	H	90
42f	OMe	H	H	H	OH	H	86
42g	OH	H	H	H	OMe	H	83
42h	*s*-Bu	H	H	H	OMe	H	92
42i	OBz	H	H	H	OBz	H	92
42j	OEt	H	H	H	OMe	H	93
42k	OBz	H	H	H	OMe	H	91
42l	OH	H	H	*i*-Pr	OH	*i*-Pr	77
42m	OEt	H	H	*i*-Pr	OEt	*i*-Pr	95
42n	OMe	H	OMe	H	OMe	H	90
42o	OMe	H	OH	H	OMe	H	72
42p	OMe	H	OH	H	OH	H	68
42q	OMe	OMe	OMe	H	OMe	H	89
42r	OMe	H	Me	H	H	H	93

cyclocondensation. The use of the developed synthetic strategy makes it possible to access pyrimido[1,2-*a*]-benzimidazole derivatives **42a**–**r** in high yields.

Another example of the construction of the pyrimidobenzimidazole system by condensation of aminobenzimidazole with unsaturated carbonyl compounds was demonstrated in a study the authors of which synthesized a series of 4-arylpyrimido[1,2-*a*]benzimidazoles **44a**–**d** by cyclization of methyl cinnamates **43a**–**d** with 2-aminobenzimidazole (**1a**) in DMF in the presence of K_2CO_3 (Scheme 12).[54] The research team points to the regioselectivity of the process and postulates the formation of only 4-substituted pyrimidobenzimidazoles.

Scheme 12



44 a R = H (47%), **b** R = 2-F (45%),
c R = 2-Cl (44%), **d** R = 2-Br (41%)

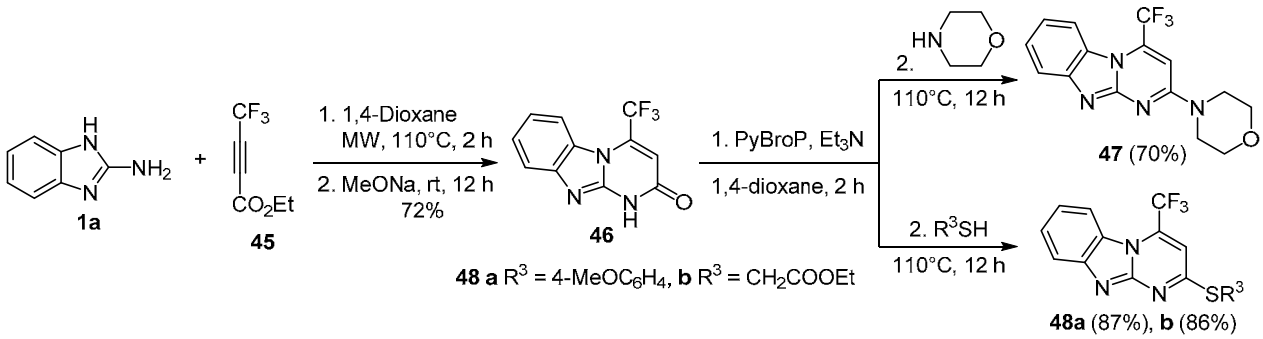
Unsaturated carbonyl compounds are not limited to derivatives containing an ethylene moiety. A nontrivial method for constructing the pyrimidobenzimidazole fragment was proposed by researchers from France. They developed a simple and convenient method for the regioselective synthesis of fluorinated pyrimido[1,2-*a*]-benzimidazole **46** by condensation of ethyl 4,4,4-trifluorobut-2-inoate (**45**) with 2-aminobenzimidazole (**1a**). Pyrimido[1,2-*a*]benzimidazolone **46** thus obtained was subsequently used to obtain a number of new 2-amino- and 2-mercaptopyrimido[1,2-*a*]benzimidazoles **47**, **48a**,**b** (Scheme 13).[55] In addition, compounds **47**, **48** are relevant as participants in further functional transformations.

Thus, due to the wide variety of components for condensation with the participation of 2-aminobenzimidazole, as well as the existence of effective catalytic systems, the creation of pyrimidobenzimidazoles based on α,β-unsaturated carbonyl compounds can be considered an effective approach.

Mono- and dicarbonyl compounds together with their derivatives are important substrates for the formation of a pyrimidine fragment in the structure of condensed pyrimidobenzimidazoles. Fang et al. developed an efficient, not using metal catalysts method for the synthesis of benzimidazo[1,2-*a*]quinazoline derivatives **51a**–**i**, **52a**–**c** involving the step of *ipso* substitution of halogen in arylcarbonyl compounds **49a**–**i**, **50a**–**c** (Scheme 14).[56] Thus, derivatives of 2-fluoro-, 2-chloro-, 2-bromo-, and 2-nitro-substituted arylaldehydes **49a**–**i** and ketones **50a**–**c** are very reactive in this kind of transformations, which allows the process to be carried out with yields of target products of more than 63%. Detailed studies have been carried out to optimize the reaction conditions. It was found that the best conditions for the process is to carry out the reaction in DMF in the presence of K_2CO_3 at 135°C.

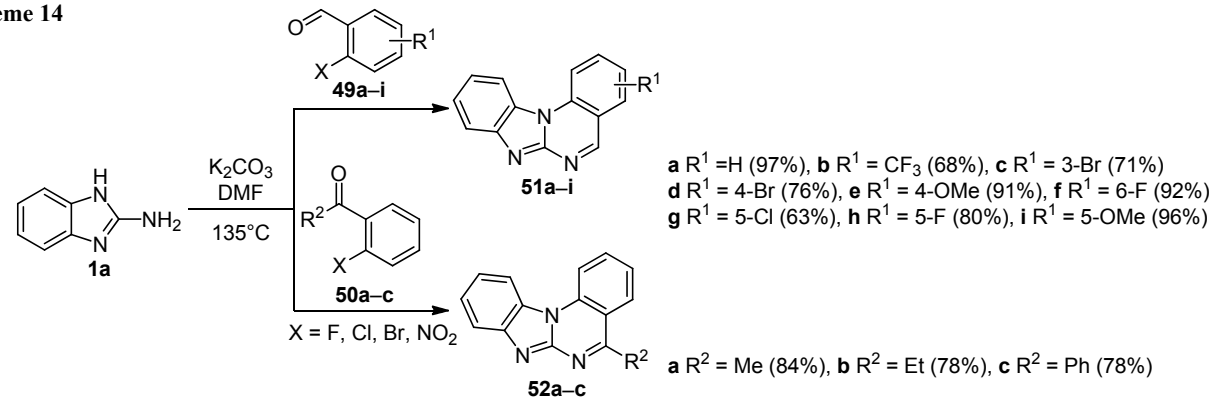
A group of Indian researchers proposed a three-step synthesis of condensed acridines **55a**–**k** containing a pyrimidobenzimidazole structural fragment.[57] At the first step, the synthesis of cyclohexanone derivative **53** from (2-amino-5-chlorophenyl)(phenyl)methanone (**52**) and cyclohexane-1,3-dione under the conditions of catalysis by

Scheme 13



48 a R^3 = 4-$MeOC_6H_4$, **b** R^3 = CH_2COOEt

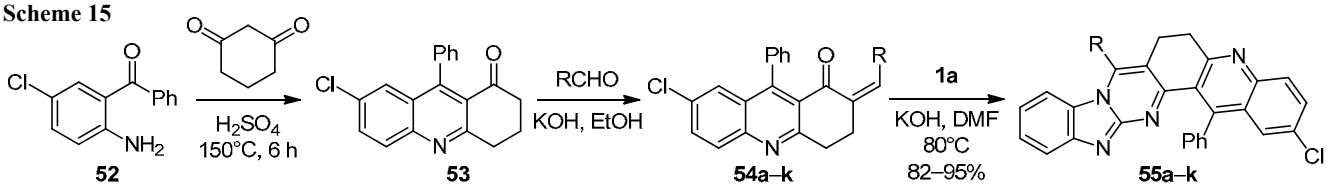
Scheme 14



a R^1 =H (97%), **b** R^1 = CF_3 (68%), **c** R^1 = 3-Br (71%)
d R^1 = 4-Br (76%), **e** R^1 = 4-OMe (91%), **f** R^1 = 6-F (92%)
g R^1 = 5-Cl (63%), **h** R^1 = 5-F (80%), **i** R^1 = 5-OMe (96%)

a R^2 = Me (84%), **b** R^2 = Et (78%), **c** R^2 = Ph (78%)

Scheme 15



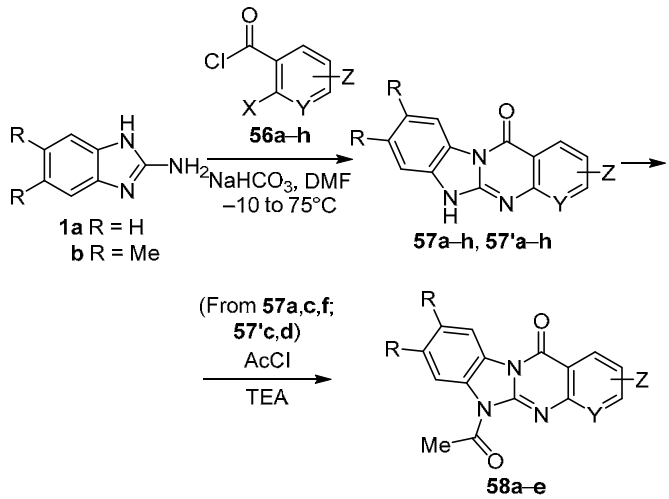
a R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-ClC_6H_4, **d** R = 4-$MeOC_6H_4$, **e** R = 4-*i*-PrC_6H_4, **f** R = 4-BrC_6H_4, **g** R = 2-BrC_6H_4, **h** R = 2,4-$(MeO)_2C_6H_3$, **i** R = 2-pyridyl, **j** R = 2-thienyl, **k** R = 2-furyl

H_2SO_4 at 150°C for 6 h is carried out. The second step is the aldol-crotonic condensation of tetrahydroacridine **53** with aromatic aldehydes, the products of which, α,β-unsaturated acridones **54a**–**k**, are reacted with 2-aminobenzimidazole (**1a**) under the conditions of catalysis by KOH. This synthesis route allowed the researchers to obtain 8-aryl-2-chloro-16-phenyl-6,7-dihydrobenzimidazo[1',2':1,2]pyrimido[4,5-*a*]acridines **55a**–**k** in 82–95% yields in the last step (Scheme 15).

The use of carboxylic acid derivatives in the synthesis of pyrimidobenzimidazoles is illustrated.[58,59] Gnanasekaran et al. have developed a method for the preparation of a series of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones and pyrido[2',3':4,5]pyrimido[1,2-*a*]benzimidazol-5(11*H*)-ones **57a**–**h** and **57'a**–**h** *via* the reaction of 2-aminobenzimidazoles **1a**,**b** with 2-haloaroyl chlorides **56a**–**h** (Scheme 16).[58] Thus, the treatment of 2-aminobenzimidazoles **1a**,**b** with acid chloride **56a**–**h** in the presence of $NaHCO_3$ in DMF at –10°C leads to acylation of the nitrogen atom of the imidazole ring. Upon subsequent heating of the reaction mixture to 75°C, an intramolecular S_NAr process occurs accompanied by the formation of the pyrimidine ring. The yields of the reaction products are 76–98%. In addition, it was found that under the conditions of the acylation reaction of the obtained compounds, the formation of only 6-acetyl isomers **58a**–**e** is observed.

Galeterone derivatives containing the pyrimidobenzimidazole fragment were successfully synthesized by the reaction of 2-aminobenzimidazoles **1a**–**c** with 16-dehydropregnenolone acetate (**59**). The target galeterone derivatives were obtained in good yields by heating under reflux in dry MeCN in the presence of *p*-TsOH (Scheme 17).[60] Under these conditions, in addition to the predominant aromatic products **60a**–**c**, **60'c**, D-homo-

Scheme 16

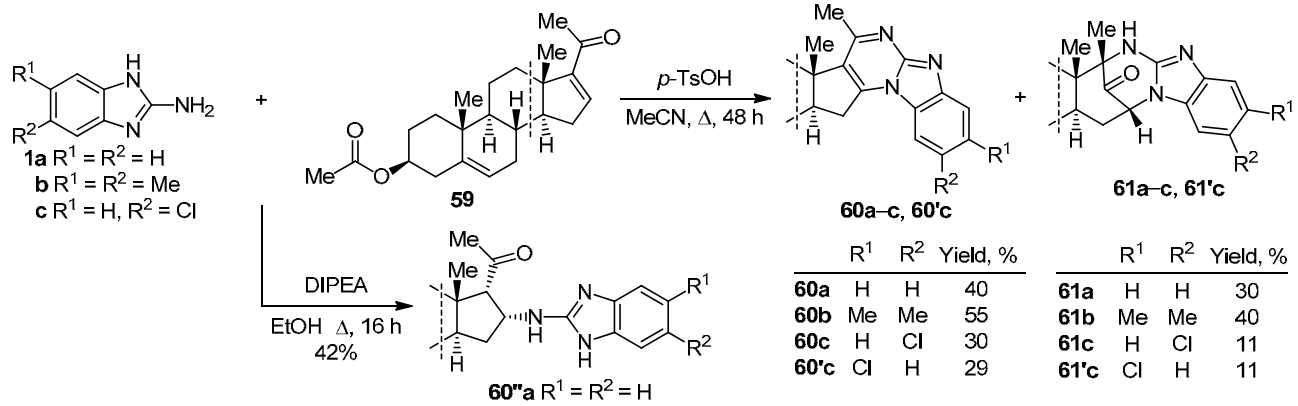


	R	X	Y	Z	Yield, %
57a/57'a	H/Me	F	CH	2-NO_2	88/91
57b/57'b	H/Me	F	CH	H	87/83
57c/57'c	H/Me	F	CH	2-F	86/87
57d/57'd	H/Me	F	CH	1-F	93/95
57e/57'e	H/Me	F	CH	1,2,3-F_3	96/98
57f/57'f	H/Me	F	CH	3-Me	76/80
57g/57'g	H/Me	F	CH	3-Br	78/84
57h/57'h	H/Me	Cl	N	H	90/95

	R	X	Y	Z	Yield, %
58a	H	F	CH	2-NO_2	94
58b	H	F	CH	2-F	96
58c	H	F	CH	3-Me	92
58d	Me	F	CH	2-F	88
58e	Me	F	CH	1-F	93

ketones **61a**–**c**, **61'c** were obtained which were formed as autoxidation products. In addition, from the mixture of derivatives **60c**, **60'c** and **61c**, **61'c**, the regioisomers were isolated as individual products. Compound **60''a** was obtained in 42% yield by lowering the reaction temperature and replacing aprotic MeCN with EtOH.

Scheme 17

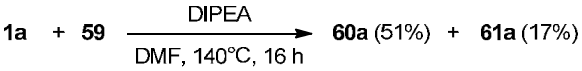


	R^1	R^2	Yield, %
60a	H	H	40
60b	Me	Me	55
60c	H	Cl	30
60'c	Cl	H	29

	R^1	R^2	Yield, %
61a	H	H	30
61b	Me	Me	40
61c	H	Cl	11
61'c	Cl	H	11

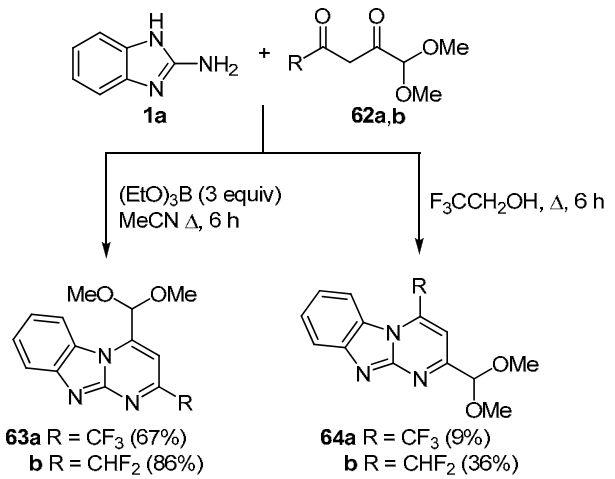
An earlier publication also investigated the reaction of 2-aminobenzimidazole (**1a**) with 16-dehydropregnenolone acetate (**59**). It was found that the reaction under basic catalysis conditions also proceeds with the formation of two derivatives **60a** and **61a** (Scheme 18).[61]

Scheme 18



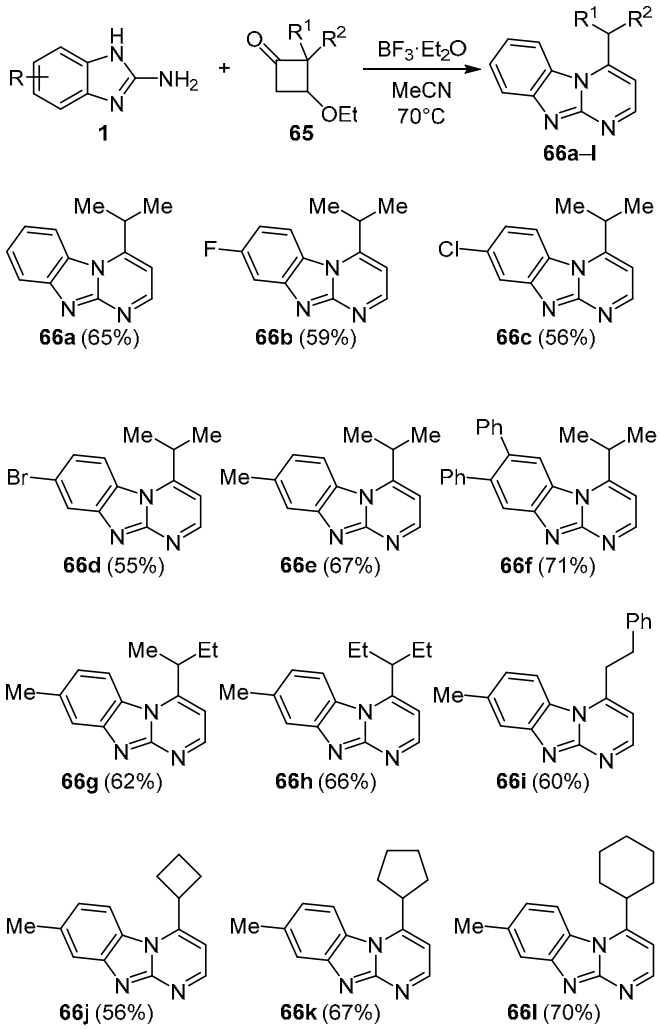
A demonstration of the use of 1,3-dicarbonyl compounds in the construction of the pyrimidobenzimidazole ring is presented in a publication from 2019. Researchers developed a simple and effective method for the synthesis of 2-polyfluoroalkylbenzimidazo[1,2-*a*]pyrimidine-4-carbaldehyde derivatives **63a**,**b** with yields of up to 86% starting from 3-(polyfluoroacetyl)pyruvaldehyde dimethyl acetal **62a**,**b** and 2-aminobenzimidazole (**1a**) (Scheme 19).[62] As the authors of the study note, the introduction of fluorinated substituents into the pyrimidobenzimidazole molecule is an effective method for changing the physical and chemical properties, as well as the biological activity of this class of compounds. The choice of reaction conditions has a decisive influence on the direction of the reaction. Thus, carrying out the reaction in MeCN in the presence of 3 equiv of $(EtO)_3B$ is characterized by high regioselectivity (98%) in favor of 2-fluoroalkyl-substituted acetals of pyrimido[1,2-*a*]benzimidazole-4-carbaldehydes **63a**,**b**. When trifluoroethanol is used without the presence of a Lewis acid, 4-fluoroalkyl derivatives **64a**,**b** are formed.

Scheme 19



Kong et al. successfully synthesized a number of pyrimido[1,2-*a*]benzimidazole derivatives **66a**–**l** *via* a chemoselective reaction of 2-aminobenzimidazoles **1** with 3-ethoxycyclobutanones **65** under the conditions of catalysis by Lewis acid $BF_3 \cdot Et_2O$. The researchers found that when using monohalogenated 2-aminobenzimidazoles **1**, the formation of regioisomeric products is observed (similar to Scheme 19, according to ^1H NMR spectroscopy), whereas in the case of unsubstituted and 5-methyl-

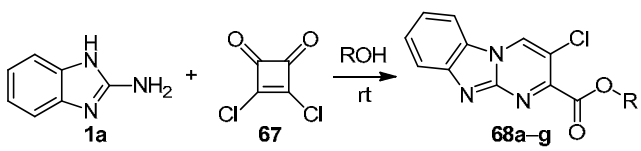
Scheme 20



aminobenzimidazoles, the process proceeds regioselectively. In addition, it was noted that the developed approach can be easily scaled without decrease of the yield of the target products (Scheme 20).[63]

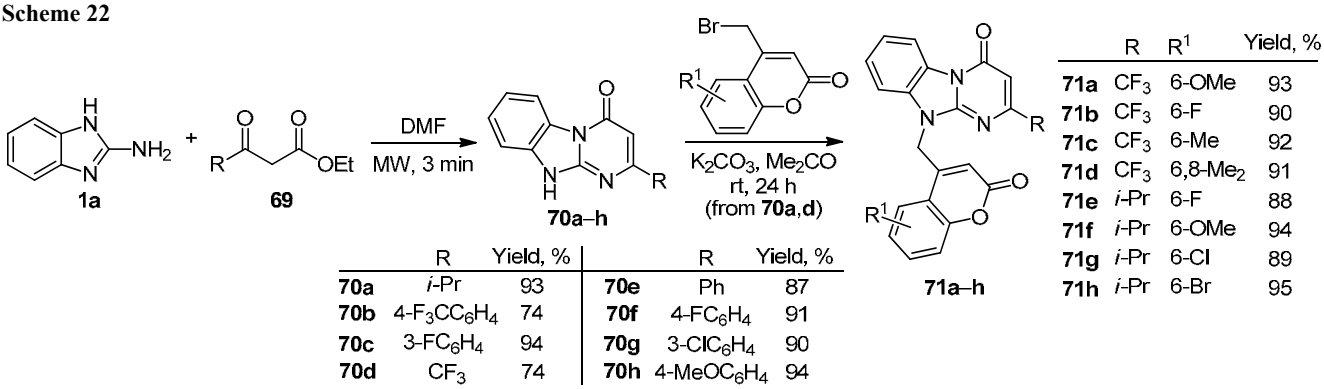
The above approach to the construction of the pyrimidobenzimidazole structure using cyclic ketones is not the only example of the use of this kind of carbonyl compounds. Thus, a group of Chinese researchers used squaraic acid chloride (**67**) in the synthesis of a series of alkyl 2-chloropyrimido[1,2-*a*]benzimidazole-3-carboxylates **68a**–**g** (Scheme 21).[64] Remarkably, the study revealed that the reaction proceeds in various alcohols with the

Scheme 21



68 **a** R = Me (52%), **b** R = Et (46%), **c** R = Pr (41%),
d R = *i*-Pr (trace), **e** R = *n*-Bu (38%),
f R = *t*-Bu (trace), **g** R = Bz (35%)

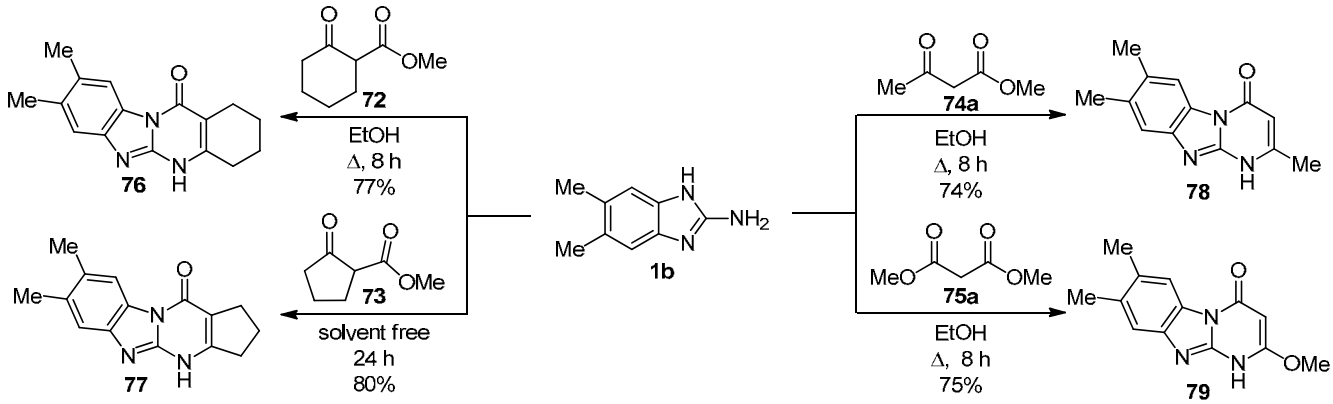
Scheme 22



	R	Yield, %		R	Yield, %
70a	*i*-Pr	93	**70e**	Ph	87
70b	4-$F_3CC_6H_4$	74	**70f**	4-FC_6H_4	91
70c	3-FC_6H_4	94	**70g**	3-ClC_6H_4	90
70d	CF_3	74	**70h**	4-$MeOC_6H_4$	94

	R	R^1	Yield, %
71a	CF_3	6-OMe	93
71b	CF_3	6-F	90
71c	CF_3	6-Me	92
71d	CF_3	6,8-Me_2	91
71e	*i*-Pr	6-F	88
71f	*i*-Pr	6-OMe	94
71g	*i*-Pr	6-Cl	89
71h	*i*-Pr	6-Br	95

Scheme 23



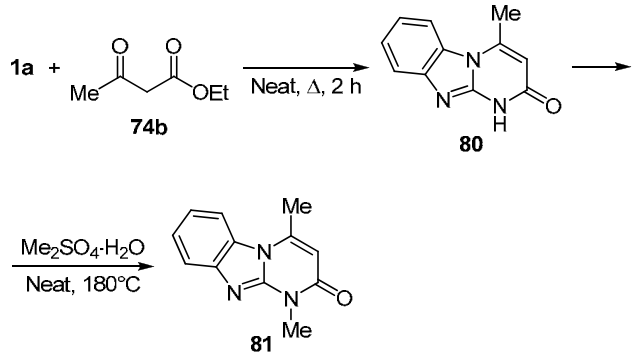
formation of the corresponding alkyl derivatives of pyrimidobenzimidazole carboxylates **68a**–**g**, while in aprotic solvents (MeCN, THF, and DMF) the reaction mixture underwent resinification and individual reaction products could not be isolated due to the extreme instability of the squaraic acid derivative and the resulting intermediates.

Keto esters and their derivatives are another important synthon in the series of 1,3-dicarbonyl compounds for the construction of the pyrimidine ring. A method was developed for the synthesis of a wide range of pyrimido-[1,2-*a*]benzimidazol-4-one derivatives **70a**–**h** by cyclo-condensation of β-keto esters **69** with 2-amino-benzimidazole (**1a**) under the conditions of microwave activation.[65] Of note is the high yields of products (74–94%) as well as a short reaction time (3 min). In addition, a number of derivatives **71a**–**h** containing a methylene-coumarin fragment in their molecules were synthesized on the basis of the obtained compounds (Scheme 22).

In addition to the above approach, a group of authors in 2015 published data on the condensation of various β-keto esters **72**–**75** with 2-amino-5,6-dimethylaminobenz-imidazole (**1b**).[66] The reactions were carried out by heating under reflux in EtOH, and in all cases good yields of the corresponding pyrimido[1,2-*a*]benzimidazoles **76**–**79** were attained (Scheme 23). The only drawback of this method is the long reaction time (8–24 h) in comparison with the conditions shown in Scheme 22. It should be noted that in both cases the formation of pyrimido[1,2-*a*]benzimidazol-4-ones was noted; however, the formation of pyrimido-[1,2-*a*]benzimidazol-2-ones can also be assumed.

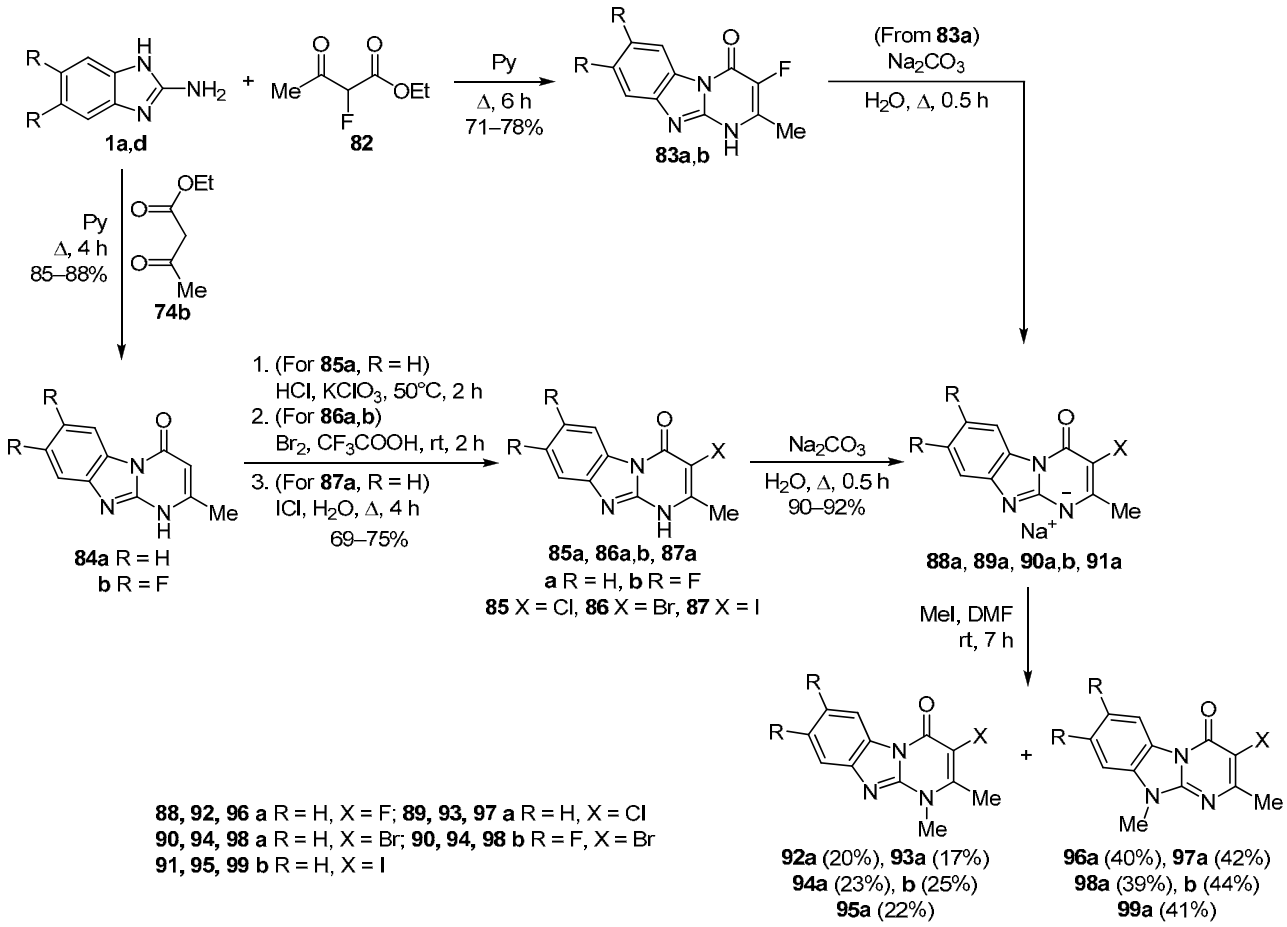
This is confirmed by a study on the synthesis of 1,4-di-methylpyrimido[1,2-*a*]benzimidazol-2(1*H*)-one (**81**), obtained by alkylation of pyrimidobenzimidazole **80** with dimethyl sulfate hydrate. In addition, the study provides detailed data on the properties of compound **81** revealed by X-ray structural analysis and quantum-chemical calculations (Scheme 24).[67]

Scheme 24

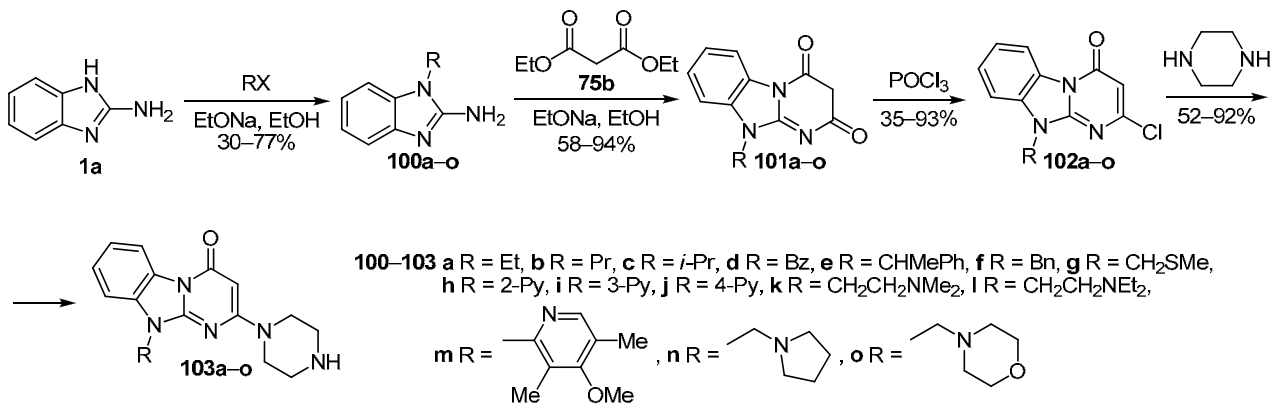


The use of ethyl acetoacetate derivatives **74b** and **82** for the construction of the pyrimidobenzimidazole structure was demonstrated. Methods for the synthesis of halo-genated 2-methylpyrimido[1,2-*a*]benzimidazol-4(10*H*)-ones **83a**,**b**, **84a**,**b**, **85a**, **86a**,**b**, **87a** were developed, the alkylation of their sodium salts **88a**, **89a**, **90a**,**b**, **91a** was studied, and the structure of the regioisomeric methylation products **92a**, **93a**, **94a**,**b**, **95a**, **96a**, **97a**, **98a**,**b**, **99a** was

Scheme 25



Scheme 26

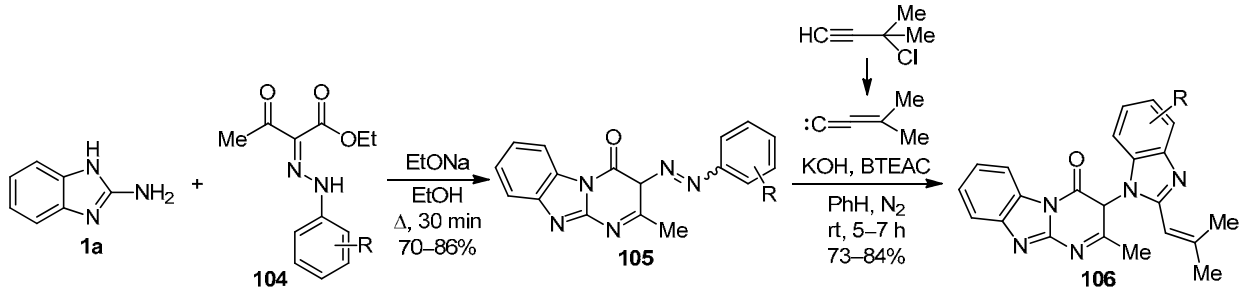


established (Scheme 25).[68] Regioisomeric pairs **92a/96a**, **93a/97a**, **94a/98a**, **94b/98b**, **95a/99a** were resolved using column chromatography.

An example of the use of dibasic acid esters described by a team of Italian researchers is the multistep synthesis of novel 10-substituted 2-(1-piperazinyl)pyrimido[1,2-*a*]-benzimidazol-4-ones **103a**–**o** using malonic ester **75b**.[69] The synthetic strategy included the initial alkylation of 2-aminobenzimidazole (**1a**), condensation of the obtained products **100a**–**o** with malonic ether **75b** effected by EtONa, chlorodeoxygenation of the obtained pyrimidobenzimidazole-2,4-diones **101a**–**o**, and nucleophilic *ipso* substitution of the halogen in compounds **102a**–**o** by the piperazine moiety (Scheme 26).

Derivatives of keto esters are also widely used in the synthesis of the pyrimidine moiety. A publication from 2011 presents the results of the synthesis of new 3-benzimidazolylpyrimidobenzimidazoles **106** under conditions of phase-transfer catalysis by benzyltriethyl-ammonium chloride (BTEAC). Initially, the condensation of benzimidazole **1a** with hydrazones of ethyl acetoacetate **104** was carried out, as a result of which pyrimido-benzimidazoles **105** were obtained. The subsequent reaction of azo derivatives **105** with carbene obtained *in*

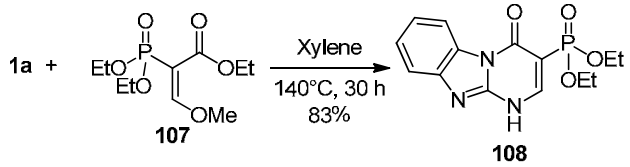
Scheme 27



situ from 3-chloro-3-methylbut-1-yne in a basic medium completes the transformation (Scheme 27).[70]

Derivatives of bifunctional compounds containing an active methylene group which are widely used in the synthesis of pyrimidobenzimidazole derivatives deserve special attention. A study of Polish researchers was devoted to the reaction of 2-diethoxyphosphoryl-3-methoxyacrylate (**107**) with aza-heterocycles, including 2-aminobenzimidazole (**1a**). It was shown that carrying out the reaction in xylene at 140°C for 30 h leads to the formation of the final pyrimidobenzimidazolone **108**.[71] The relatively mild conditions under which pyrimidinone **108** is formed, in comparison with other considered heterocycles, clearly reflect the higher nucleophilicity of the nitrogen atom of benzimidazole which favors intramolecular *N*-acylation (Scheme 28).

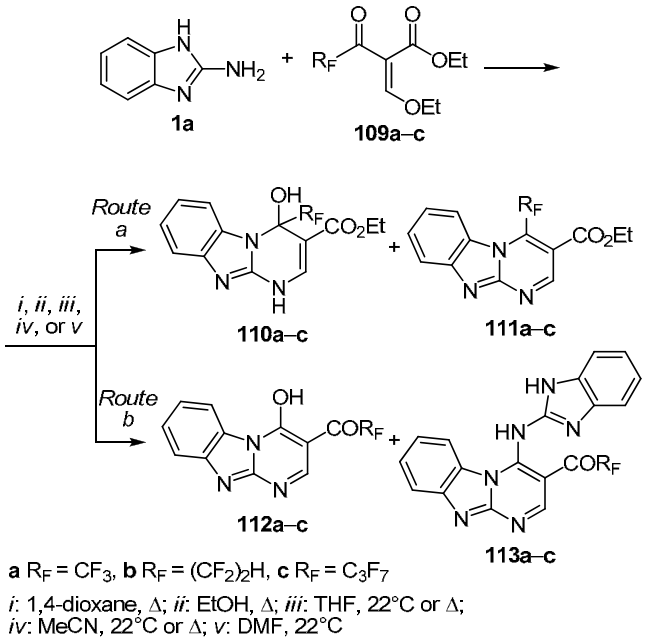
Scheme 28



The publication of Russian researchers is yet another demonstration of the use of α-alkoxymethylene derivatives of keto esters (by the example of compounds **109a–c**). The authors report on the regiodirected synthesis of polyfluoroalkyl derivatives of benzimidazopyrimidines **110–113 a–c**, as well as the route of the process depending on the fluoroalkyl substituent (Scheme 29).[72]

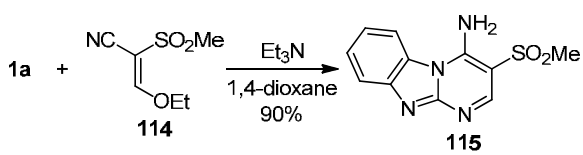
It was found that the nature of the solvent used and the size of the fluoroalkyl moiety have a decisive influence on the ratio of the resulting compounds. Thus, for 2-ethoxymethylidene-4,4,4-trifluoroacetoacetate (**109a**), cyclization *via* route *a* is preferable in 1,4-dioxane, whereas in polar solvents this cyclization route becomes the only one. Tetrafluoroethyl-containing ester **109b** shows such selectivity only in polar aprotic solvents, while in proton-donating EtOH and weakly polar 1,4-dioxane, the formation of pairs of reaction products **110b**/**111b** and **112b**/**113b** in about equal total yields is observed which indicates that realization of heterocyclization routes *a* and *b* are equally probable. At the same time, the reaction of heptafluoropropyl-substituted ester **109c** is characterized by a complete lack of selectivity since, regardless of the solvent used, cyclization proceeds along both routes (*a* and *b*).

Scheme 29



A recent study reports the use of 3-ethoxy-2-methylsulfonylacrylonitrile (**114**) in the synthesis of novel aminomethylsulfonylpyrimidines. In particular, the reaction of compounds **1a** and **114** in 1,4-dioxane in the presence of Et_3N yielded 4-amino-3-(methylsulfonyl)pyrimido[1,2-*a*]-benzimidazole (**115**) (Scheme 30).[73]

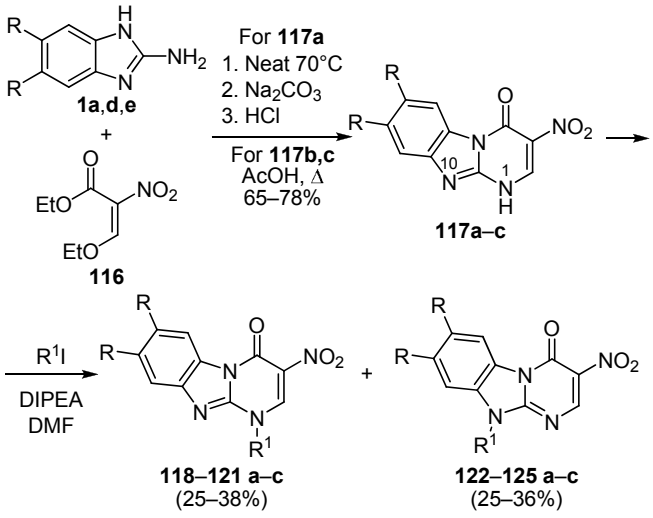
Scheme 30



An example of the creation of nitro derivatives of pyrimidobenzimidazoles is the synthesis of 3-nitropyrimido-[1,2-*a*]benzimidazol-4-ones **117a–c** and a detailed study of the alkylation of these derivatives described in a publication from 2017. Based on the studies carried out, it was found that alkylation proceeds at the N-1 and N-10 atoms with the formation of two series of regioisomeric products **118–121 a–c** and **122–125 a–c**, respectively

(Scheme 31). In addition, the ratio of regioisomers was determined, which depends on the nature of the used alkyl iodide. In the case of alkylation with methyl, ethyl, or *n*-propyl iodide, the ratio of the products of 1- and 10-substitution is 1:0.7. In the reaction with isopropyl iodide, this ratio is 1:0.5.[74]

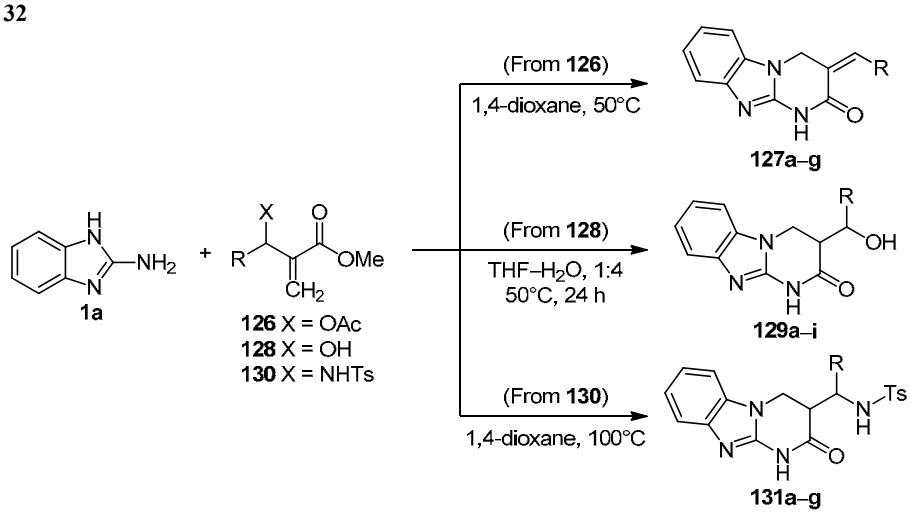
Scheme 31



1 a R = H, **d** R = F, **e** R = Cl
118–125 a R = H, **b** R = F, **c** R = Cl
118, **122** R^1 = Me; **119**, **123** R^1 = Et;
120, **124** R^1 = Pr; **121**, **125** R^1 = *i*-Pr

Wong and colleagues presented a series of publications on the synthesis of pyrimidobenzimidazoles **127**, **129**, **131** *via* the reaction of 2-aminobenzimidazole (**1a**) with Baylis–Hillman acetates, alcohols, and amines **126**, **128**, **130**, respectively.[75–77] The methods presented by the authors assume varying conditions, catalysts, and reagents (Scheme 32).

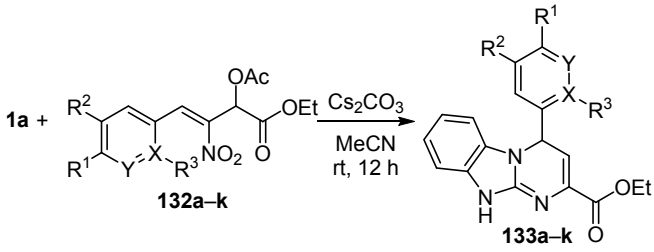
Scheme 32



127 a R = Ph (85%), **b** R = 4-ClC_6H_4 (93%), **c** R = 2-Fur (76%), **d** R = 2-$F_3CC_6H_4$ (90%), **e** R = 3-BrC_6H_4 (97%), **f** R = 3-$MeOC_6H_4$ (90%), **g** R = cyclopropyl (71%)
129 a R = 4-ClC_6H_4 (89%), **b** R = 4-FC_6H_4 (95%), **c** R = 4-$NO_2C_6H_4$ (81%), **d** R = 2-Fur (80%), **e** R = 3-$O_2NC_6H_4$ (77%), **f** R = 2-$O_2NC_6H_4$ (74%), **g** R = 4-MeC_6H_4 (91%), **h** R = 2-$F_3CC_6H_4$ (90%), **i** R = Ph (90%)
131 a R = Ph (86%), **b** R = 4-FC_6H_4 (91%), **c** R = 4-ClC_6H_4 (94%), **d** R = 4-$O_2NC_6H_4$ (81%), **e** R = 3-$O_2NC_6H_4$ (97%), **f** R = 2-$O_2NC_6H_4$ (96%), **g** R = 4-MeC_6H_4 (75%)

By changing the catalyst and solvent, a team of Indian researchers obtained pyrimidobenzimidazole derivatives **133a–k** *via* the reaction of Morita–Baylis–Hillman acetates **132a–k** and 2-aminobenzimidazole (**1a**) (Scheme 33).[78]

Scheme 33

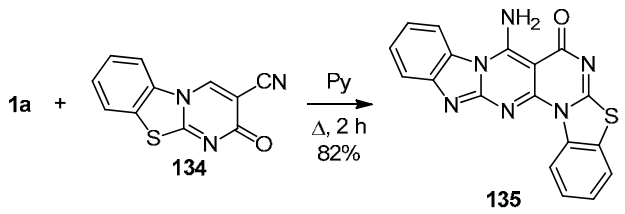


133 a R^1 = R^2 = R^3 = H, Y = CH, X = C (82%)
b R^1 = Br, R^2 = R^3 = H, Y = CH, X = C (80%)
c R^1 = Me, R^2 = R^3 = H, Y = CH, X = C (77%)
d R^1 = H, R^2 = Br, R^3 = F, Y = CH, X = C (68%)
e R^1 = Br, R^2 = H, R^3 = Cl, Y = CH, X = C (70%)
f R^1 = H, R^2 = H, R^3 = "–", Y = CH, X = N (70%)
g R^1 = H, R^2 = Br, R^3 = F, Y = N, X = C (67%)
h R^1 = OH, R^2 = R^3 = H, Y = CH, X = C (73%)
i R^1 = R^2 = H, R^3 = F, Y = CH, X = C (60%)
j R^1 = R^2 = H, R^3 = NO_2, Y = CH, X = C (51%)
k R^1 = H, R^2 = CF_3, R^3 = H, Y = CH, X = C (72%)

Another approach for the construction of polycyclic derivatives of pyrimidobenzimidazoles is the synthesis of hexacyclic derivative **135** was demonstrated in a publication from 2014.[79] Compound **135** was obtained by annulation of 2-aminobenzimidazole (**1a**) and benzothiazolopyrimidine **134** (Scheme 34). The authors of this paper paid much attention to the study of the mechanism and regioselectivity of the process.

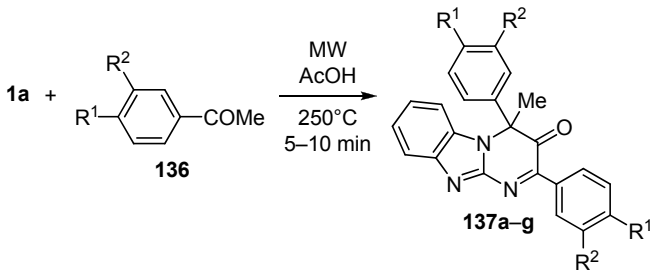
As mentioned earlier, reactions catalyzed by microwave irradiation are quite common and relevant in condensation

Scheme 34



processes that take place with the elimination of low molecular weight compounds (H_2O, alcohols, etc.). Adhering to this approach, a method was developed for the synthesis of pyrimidobenzimidazolone derivatives **137a**–**g** based on 2-aminobenzimidazole (**1a**) and phenylethanones **136** (Scheme 35).[80]

Scheme 35



137 a $R^1 = R^2 = H$ (81%); **b** $R^1 = Me$, $R^2 = H$ (72%)
c $R^1 = H$, $R^2 = Me$ (86%); **d** $R^1 = OMe$, $R^2 = H$ (70%)
e $R^1 = H$, $R^2 = OMe$ (92%); **f** $R^1 = Br$, $R^2 = H$ (93%)
g $R^1 = H$, $R^2 = Br$ (88%)

To conclude, the methods for constructing a pyrimidobenzimidazole scaffold based on bifunctional synthetic equivalents have on the whole been developed in sufficient detail, although it cannot be said that they are completely exhausted.

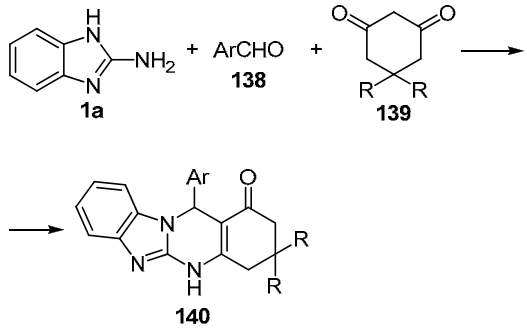
Construction of pyrimidobenzimidazole structure by multicomponent reactions

Among the methods for constructing the azolopyrimidine fragment, multicomponent reactions (MCRs) occupy a special place. Due to its simplicity in application and wide possibilities for varying all components, MCRs open unconventional synthetic routes for the creation of new hard-to-access heterocyclic molecular structures. In the literature, examples of the use of MCR for the synthesis of pyrimidobenzimidazoles are represented by three-component reactions, the main components of which are derivatives of benzimidazoles and aldehydes. The third component is labile and is often an active CH component. This section of the review is systematized according to the variation of the third component of an MCR.

The development of new catalytic systems and determination of their efficiency in MCR was the goal of a large number of studies related to the development of MCR methodology.[81–96] The use of new catalysts and their systems allows: simplifying the procedure for obtaining the target product, increasing the selectivity of the process, reducing its cost, and making it less environmentally harmful due to the use of nontoxic solvents. The latter condition is of particular importance for the use of the method in the pharmaceutical industry when the environmental friendliness of production and the purity of the resulting medicinal compound come to the fore as criteria for assessing the possibility of its technological application.

Numerous studies[81–101] present the synthesis of pyrimidobenzimidazole derivatives **140** by the three-component reaction of 2-aminobenzimidazole (**1a**), aromatic aldehyde derivatives **138**, and cyclohexane-1,3-diones **139** (Scheme 36). Considering the uniformity of the synthetic route used in the presented publications, special attention is paid to the development and study of various catalytic systems.

Scheme 36



A team of Iranian scientists describe the use of sulfamic acid as a reusable green catalyst under the conditions of heating in MeCN for the synthesis of derivatives **140** (Table 3). It was noted that the use of sulfamic acid as a catalyst provides certain advantages, including ease of use, ease of isolation, and good product yields, as well as the possibility of its reuse.[81]

Table 3. Examples of NH_2SO_3H-catalyzed three-component reaction of compounds **1a**, **138**, and **139** to obtain compounds **140**

Entry	Ar	R	Reaction time, min	Yield, %
1	Ph	Me	15	94
2	4-ClC_6H_4	Me	15	90
3	4-BrC_6H_4	Me	15	90
4	4-$MeOC_6H_4$	Me	18	90
5	4-HOC_6H_4	Me	20	90
6	4-$O_2NC_6H_4$	Me	18	95

For the synthesis of derivatives **140**, catalytic systems were developed in the form of modified Fe_3O_4 nanoparticles containing:[82–87]

– silica with terminal sulfo groups;[82]
– L-proline fragments;[83]
– chitosan structures;[84]
– starch with *n*-butylsulfo group;[85]
– titanium dioxide functionalized with sulfo groups;[86]
– system $Cu@Fe_3O_4$.[87]

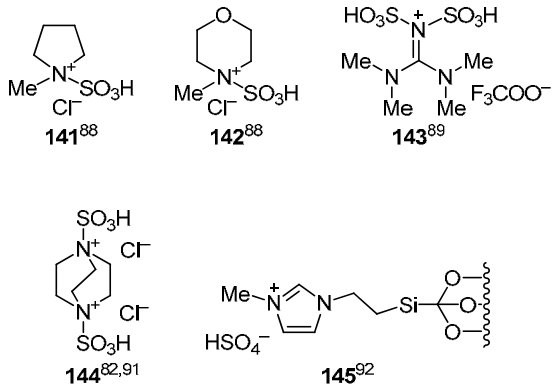


Figure 3. Ionic liquids used in MCR synthesis of pyrimido-[1,2-*a*]benzimidazoles **140**.

Among the advantages of these catalysts are high efficiency (yields of derivatives **140** of over 90%), reusability, and compliance with the principles of green chemistry. In addition, one of the main features of these catalytic systems is their magnetic activity, which makes it possible to separate the catalyst from the reaction mixture using an external magnet.

Another group of catalysts used for MCR shown in Scheme 36 are ionic liquids **141**–**145** (Fig. 3).[88–92] Among the advantages of the considered catalysts are their cheapness, ease of preparation, and high stability. In addition, the research emphasizes the possibility of reuse of catalysts without losing their activity. In addition, it should be noted that the significant reduction in the reaction time and high yields of derivatives **140** make these catalysts attractive for many other studies in the field of synthesis of various nitrogenous heterocycles. While not proven, they are assumed to be of a general nature.

A series of studies was devoted to the use of acid catalysts in the synthesis of derivatives **140**.[93–96] Considered among the catalysts are polyvinylpyrrolidonium hydrogen sulfate,[93] $(CH_2)_4(DABCO–SO_3H)_2Cl_4$ nanoparticles,[94] PTSA,[95] and AcOH.[96] Among the advantages of using this series of catalysts, high yields of reaction products, ease of use, and environmental friendliness of the process are given.

The main tasks for optimizing the conditions for carrying out any synthetic process, along with increasing the yield of the target product, include the reduction of the reaction time. Microwave radiation is used to intensify many reactions in organic chemistry. From this point of view, the implementation of the process as shown in Scheme 36 under microwave irradiation conditions without solvent and catalysts,[97] as well as under the conditions of catalysis by $Sc(OTf)_3$[98] is of great synthetic importance.

In 2016, the synthesis of derivatives **140** using a deep eutectic solvent **146**, which is a mixture of choline chloride and glycerol was described (Fig. 4).[99] Along with high yields, short reaction times, and mild reaction conditions, the main advantage of the investigated solvent is its biodegradability.

The synthesis of a number of novel condensed tetracyclic thiopyrano[3,4:4,5]pyrimido[1,2-*a*]benzimidazol-

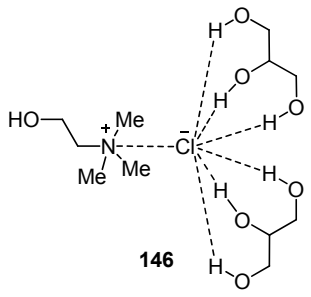
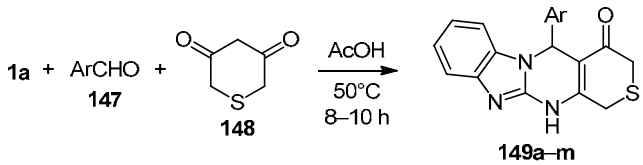


Figure 4. The structure of solvent **146**.

4-ones **149a**–**m** from 2-aminobenzimidazole (**1a**), aromatic aldehydes **147**, and thio derivative **148** (as an active CH component) was investigated.[100] The process was carried out under the conditions of heating the components in an AcOH medium at 50°C for 8–10 h (Scheme 37).

Scheme 37



	Ar	Yield, %		Ar	Yield, %
149a	Ph	82	**149g**	3,4-$Cl_2C_6H_3$	84
149b	4-BrC_6H_4	82	**149h**	3-$O_2NC_6H_4$	85
149c	2-FC_6H_4	77	**149i**	4-$O_2NC_6H_4$	85
149d	4-FC_6H_4	80	**149j**	4-MeC_6H_4	84
149e	2-ClC_6H_4	73	**149k**	3-$MeOC_6H_4$	76
149f	3-ClC_6H_4	75	**149l**	4-$MeOC_6H_4$	80
			149m	3,4,5-$(MeO)_3C_6H_2$	85

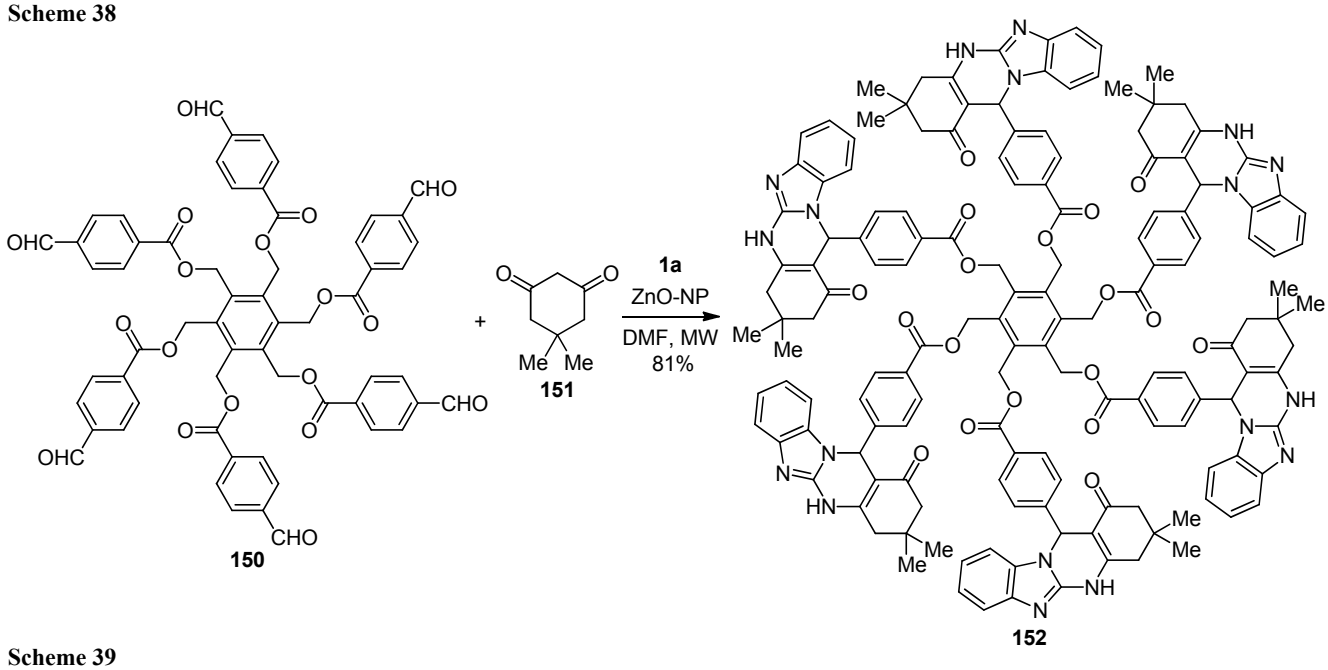
Another interesting example was demonstrated in the work of Egyptian researchers by a method of obtaining poly(tetrahydrobenzimidazo[2,1-*b*]quinazolin-1-one) **152** by multicomponent condensation of 2-aminobenzimidazole (**1a**), polyaldehyde **150**, and dimedone (**151**) in DMF catalyzed by ZnO nanoparticles under the conditions of microwave radiation (Scheme 38).[101]

A innovative method for constructing benzimidazo-quinazolinone structures **154a**–**h** is presented in a publication from 2016.[102] The difference between this approach and the above is that benzyl halide derivatives **153** which are oxidized with trimethylamine *N*-oxide are used instead of an aromatic aldehyde (Scheme 39).

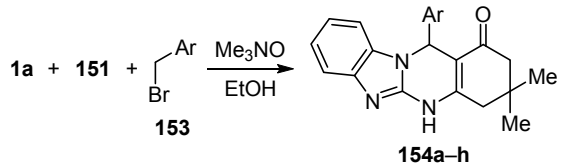
A large number of studies[103–120] devoted to the synthesis of pyrimidobenzimidazoles **157** using MCR of keto esters and their various derivatives **155** as well as malononitrile (**156**) are presented in general in Scheme 40.

A series of publications[103–106] was devoted to the study of MCRs of malononitrile (**156**), 2-aminobenzimidazole (**1a**), and aromatic aldehydes **138**. Alum[103] was used as a condensation catalyst; at the same time PTSC was successfully used,[104] and Mexican researchers carried out the synthesis by heating the components under reflux in H_2O.[105] In addition, the successful use of polyvinyl-pyrrolidonium perchlorate as a highly efficient catalyst in

Scheme 38

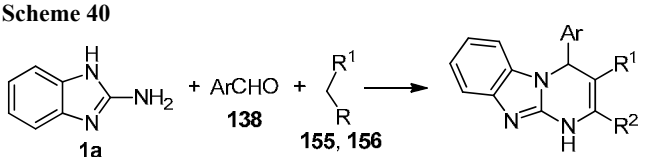


Scheme 39



154 a Ar = 3-NCC_6H_4 (94%), **b** Ar = 4-ClC_6H_4 (92%),
c Ar = Ph (90%), **d** Ar = 4-BrC_6H_4 (92%),
e Ar = 3,5-$(MeO)_2C_6H_4$ (88%), **f** Ar = 2,4,6-$(MeO)_3C_6H_4$ (88%),
g Ar = 4-$O_2NC_6H_4$ (96%), **h** Ar = 4-HOC_6H_4 (85%)

Scheme 40



155 R = AlkCO, ArCO
R^1 = CN, CO_2Alk, Me
156 R = R^1 = CN

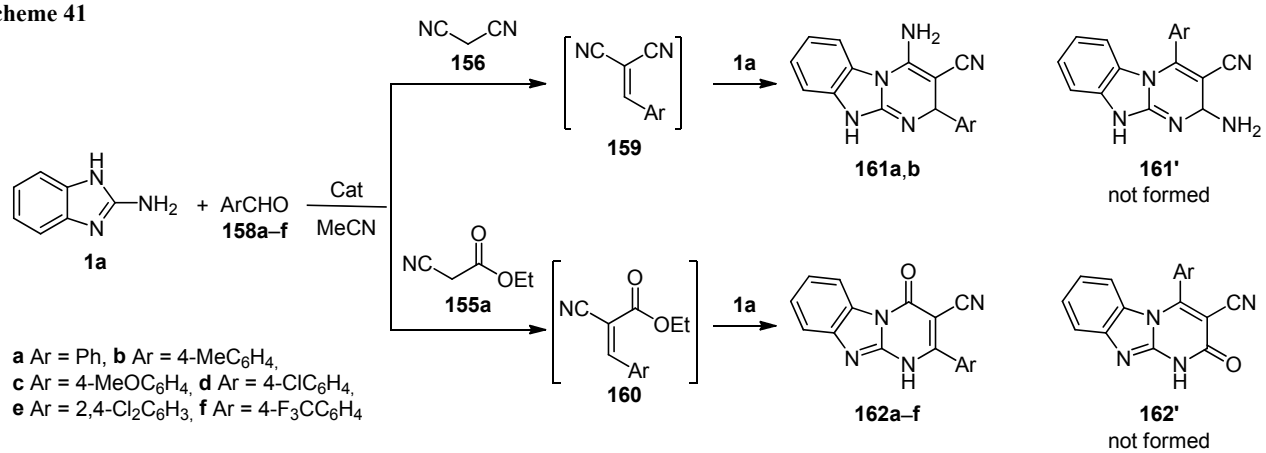
R^1 = CN, CO_2Alk, Me
R^2 = NH_2, Alk, Ar

the preparation of 1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives **157** (R^1 = NH_2, R^2 = CN) is reported.[106]

The selectivity of the process of the MCR of 2-aminobenzimidazole (**1a**), aromatic aldehydes **158a**–**f**, ethyl cyanoacetate (**155a**), and malononitrile (**156**) (Scheme 41) was studied.[108,109] In the above studies, compounds exhibiting basic properties were investigated as condensation catalysts: NaOAc, Et_3N, and MgO. It has been shown that their use provides high yields and product purity. In addition, it is noted that in this case the reaction proceeds selectively with the formation of products **161a**,**b** and **162a**–**f**. The regioselectivity of the process is explained by the formation of the Knoevenagel condensation products **159** and **160**, the further reaction of which with aminobenzimidazole **1a** is due to the increased electrophilicity of the methylene and ethoxycarbonyl fragments. As a result, the reaction products **161'** and **162'** are not preferred in the given process conditions.

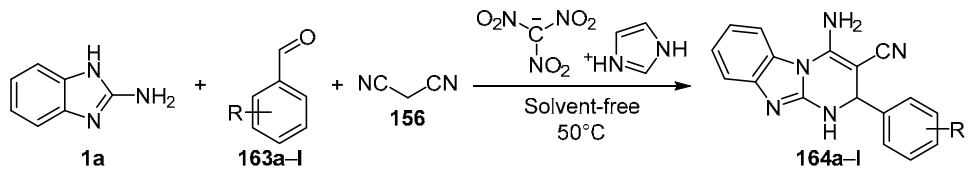
Another example of a MCR using malononitrile (**156**) and aromatic aldehydes **163a**–**l** was described in 2018.[110] It is noteworthy that the developed approach uses a nanostructured ionic liquid, a salt of imidazole and trinitromethane $[HIMI]C(NO_2)_3$ (Scheme 42). As noted by the authors, the use of this catalyst significantly reduces the

Scheme 41



a Ar = Ph, **b** Ar = 4-MeC_6H_4,
c Ar = 4-$MeOC_6H_4$, **d** Ar = 4-ClC_6H_4,
e Ar = 2,4-$Cl_2C_6H_3$, **f** Ar = 4-$F_3CC_6H_4$

Scheme 42



164 a R = H (91%), **b** R = 2-MeO (89%), **c** R= 3-MeO (88%), **d** R = 4-Cl (93%), **e** R = 2-Cl (91%), **f** R = 2,3-Cl_2 (91%), **g** R = 3-Br (94%), **h** R = 4-F (90%), **i** R = 2-F (91%), **j** R = 4-NO_2 (90%), **k** R = 3-NO_2 (91%), **l** R = 4-CN (89%)

reaction time, increases the yields of pyrimidobenzimidazoles **164a–l**, and also allows the process to be carried out in accordance with the principles of green chemistry.

Keto esters and diketones are important substrates for the construction of the pyrimidobenzimidazole scaffold.[111–120] In these studies, the present synthetic strategy for the preparation of pyrimidobenzimidazoles corresponds to the approach shown in Scheme 36. The relevance of the research lies in demonstrating the broad capabilities of various catalysts and their systems in MCRs.

Thus, the synthesis of 1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carboxylates **169a–y** using ionic liquids **167**, **168** as catalysts and in the absence of solvents (Scheme 43) was presented.[111,112] It was noted that when using these catalysts condensation proceeded smoothly with a wide range of substrates **165**, **166**, and the products were obtained in good or excellent yields (Table 4). In addition, the low cost of catalysts and the possibility of their reuse, as well as the ease of product isolation, are the main advantages of the developed methods.

In a number of studies on the preparation of pyrimido[1,2-*a*]benzimidazoles, the catalytic activity of some natural compounds, such as L-proline,[113] thiamine hydrochloride,[114] and citric acid was investigated.[115] Along with all the advantages of organocatalysts, the described procedures are carried out in aqueous media, which expands the field of application of the MCR. At the same time, the efficiency of catalysts, a wide range of substrates used, and mild reaction conditions significantly expand the possibilities for the synthesis of relevant pyrimido[1,2-*a*]-benzimidazole derivatives.

Scheme 43

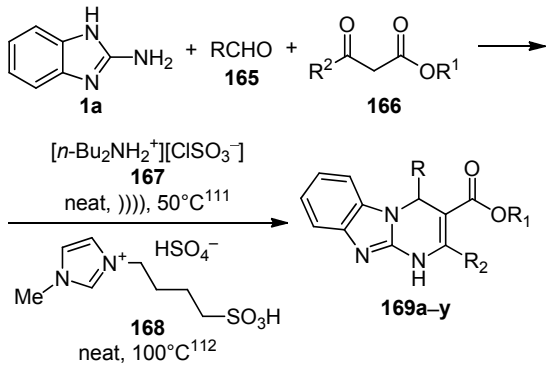


Table 4. The yields of 1,4-dihydropyrimido-[1,2-*a*]benzimidazole-3-carboxylates **169a–y**

Compound	R	R^1	R^2	Yield, %
169a	4-FC_6H_4	Et	Ph	95
169b	4-ClC_6H_4	Et	Ph	92
169c	3-ClC_6H_4	Et	Ph	91
169d	Et	*t*-Bu	Me	90
169e	Pr	*t*-Bu	Me	92
169f	2-Thienyl	*t*-Bu	Me	89
169g	4-$O_2NC_6H_4$	*t*-Bu	Me	94
169h	4-MeC_6H_4	*t*-Bu	Me	95
169i	3-ClC_6H_4	*t*-Bu	Me	91
169j	4-NCC_6H_4	Et	Me	93
169k	4-$MeOC_6H_4$	Et	Me	92
169l	1,3-Benzodioxol-5-yl	Et	Me	89
169m	4-$EtOC_6H_4$	Et	Me	93
169n	2,5-$Me_2C_6H_3$	Et	Me	91
169o	2,4-$F_2C_6H_3$	Et	Me	90
169p	2-F-5-BrC_6H_3	Et	Me	89
169q	C_6H_{11}	Et	Me	92
169r	2-F-4-BrC_6H_3	Et	Me	89
169s	2-F-4-BrC_6H_3	Me	Me	91
169t	C_6H_{11}	Me	Me	90
169u	2,4-$F_2C_6H_3$	Me	Me	91
169v	4-NCC_6H_4	Me	Me	92
169w	1,3-Benzodioxol-5-yl	Me	Me	88
169x	2-F-5-BrC_6H_3	Me	Me	90
169y	2,5-$Me_2C_6H_3$	Me	Me	91

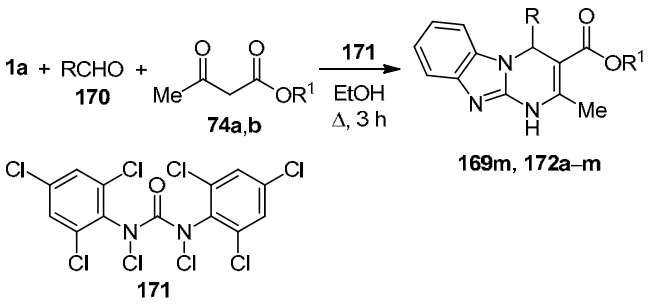
A simple and effective method for the synthesis of pyrimido[1,2-*a*]benzimidazole derivatives **169m**, **172a–m** (Table 5) using *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea (CC-2) (**171**), aromatic aldehydes **170**, and keto esters **74a**,**b** was demonstrated by Indian researchers (Scheme 44).[116] The main advantage of the method is that reagent **171** is converted during the reaction into insoluble 1,3-bis(2,4,6-trichlorophenyl)urea which can easily be separated by simple filtration and converted back to CC-2 by treatment with AcOH/Cl_2/NaOH.

Table 5. The yields of of 1,4-dihydropyrimido-[1,2-*a*]benzimidazole-3-carboxylates **169m**, **172a**–**m**

Com-pound	R	R^1	Yield, %	Com pound	R	R^1	Yield, %
169m	4-$EtOC_6H_4$	Et	78	**172g**	4-$HONC_6H_4$	Et	71
172a	4-$MeOC_6H_4$	Et	82	**172h**	4-$MeOC_6H_4$	Et	75
172b	4-EtC_6H_4	Et	76	**172i**	3-HOC_6H_4	Et	66
172c	4-Me_2CH	Et	72	**172j**	4-$Me_2NC_6H_4$	Et	65
172d	4-FC_6H_4	Et	68	**172k**	4-$F_3CC_6H_4$	Et	58
172e	4-$O_2NC_6H_4$	Et	70	**172l**	3,4,5-$(MeO)_3C_6H_2$	Me	55
172f	3-$O_2NC_6H_4$	Me	68	**172m**	Indolyl*	Me	55

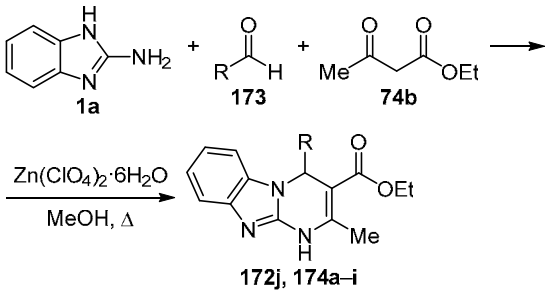
* No information is provided in the publication as to which isomer of indole aldehyde was used.

Scheme 44



In 2014, Indian researchers studied the effect of zinc perchlorate ($Zn(ClO_4)_2 \cdot 6H_2O$) on the MCR of aldehydes **173**, ethyl acetoacetate (**74b**), and 2-aminobenzimidazole (**1a**) in the synthesis of a number of pyrimido[1,2-*a*]-benzimidazole derivatives **172j**, **174a**–**i** (Scheme 45).[117] The authors note high yields of the reaction products; however, in the case of using aldehydes containing an OH group in position 2 or 4 of the phenyl ring, a decrease in the yields of the target product is observed.

Scheme 45



172j R = 4-$Me_2NC_6H_4$ (71%)

174 a R = 2-Py (73%), **b** R = 3-Py (72%), **c** R = 4-Py (70%), **d** R = 2-thienyl (71%), **e** R = 2-pyrrolyl (72%), **f** R = 2-$O_2NC_6H_4$ (72%), **g** R = 2-HOC_6H_4 (65%), **h** R = 4-HOC_6H_4 (64%), **i** R = 2-hydroxynaphthalen-1-yl (75%)

Another catalytic system used in the synthesis of pyrimido[1,2-*a*]benzimidazoles is H_3PO_4 supported on Al_2O_3.[118] Among the advantages of this catalyst are the possibility of its reuse without loss of efficiency, as well as

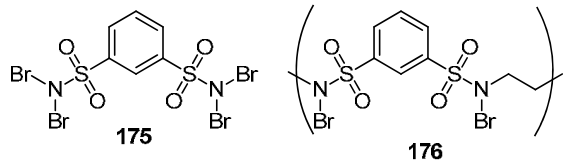
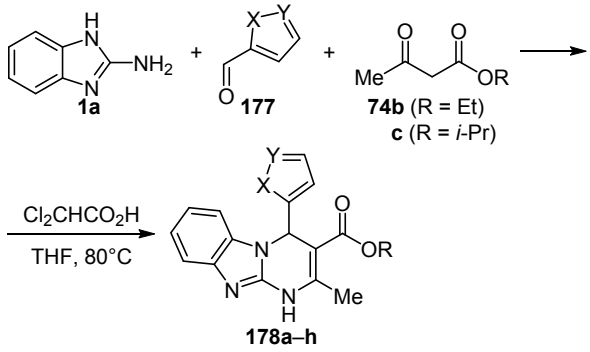


Figure 5. The structures of catalysts **175** and **176**.

carrying out the reaction without a solvent. In addition to the above approach, a team of authors from Iran reported the use of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) (**175**) and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) (PBBS) (**176**) as MCR catalysts (Fig. 5).[119] These catalysts also allow solvent-free reactions.

A method was developed for the synthesis of new adenosine receptor A_2B antagonists. Among the synthesized structures, the most significant in terms of their activity were pyrimido[1,2-*a*]benzimidazole derivatives **178a**–**h** which were synthesized *via* a MCR of aldehydes **177**, keto esters **74b**,**c**, and 2-aminobenzimidazole (**1a**).[120] Optimization of the synthesis showed that that the synergistic use of chloroacetic acid (as a catalyst) and microwave irradiation led to a significant increase in the yields of compounds **178a**–**h** (Scheme 46).

Scheme 46

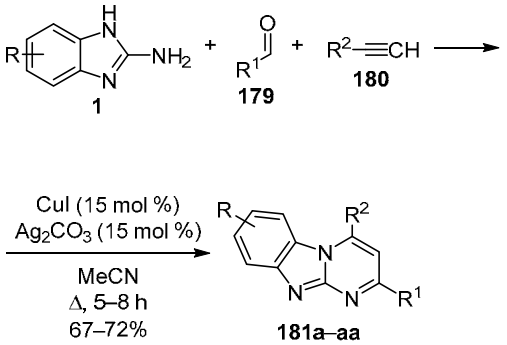


178 a R = Et, X = O, Y = CH (55%); **b** R = *i*-Pr, X = O, Y = CH (61%)
c R = Et, X = CH, Y = O (72%); **d** R = *i*-Pr, X = O, Y = CH (71%)
e R = Et, X = S, Y = CH (68%); **f** R = *i*-Pr, X = S, Y = CH (66%)
g R = Et, X = CH, Y = S (68%); **h** R = *i*-Pr, X = CH, Y = S (67%)

Among other substrates used in MCRs, derivatives of terminal alkynes are of interest.[121–123] Thus, the regioselective synthesis of pyrimido[1,2-*a*]benzimidazoles **181a**–**aa** by the reaction of 2-aminobenzimidazoles **1**, aldehydes **179**, and alkynes **180** is described. The reaction is carried out in MeCN under reflux using a copper and silver salt system as a catalyst (Scheme 47).[121]

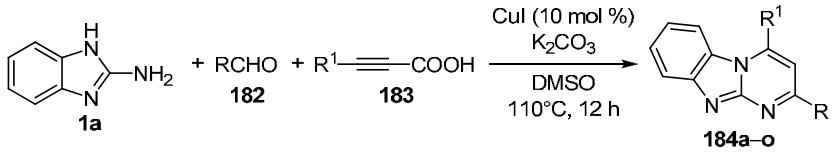
A particular example of the use of alkyne derivatives in the synthesis of pyrimido[1,2-*a*]benzimidazoles is a work by Chinese researchers.[124,125] The authors have developed an approach to the synthesis of disubstituted pyrimido-[1,2-*a*]benzimidazoles **184a**–**o** using the MCR of benzimidazole **1a**, aldehydes **182**, and alkynecarboxylic acids **183** in the presence of a catalytic amount of CuI and K_2CO_3 (Scheme 48).

Scheme 47



181 a R = H, R^1 = 4-ClC_6H_4, R^2 = Ph
b R = H, R^1 = 3,4-$Cl_2C_6H_3$, R^2 = Ph
c R = H, R^1 = 4-$O_2NC_6H_4$, R^2 = Ph
d R = H, R^1 = 3-$O_2NC_6H_4$, R^2 = Ph
e R = H, R^1 = 4-NCC_6H_4, R^2 = Ph; **f** R = H, R^1 = 4-FC_6H_4, R^2 = Ph
g R = H, R^1 = 4-BrC_6H_4, R^2 = Ph
h R = H, R^1 = 2,6-$Cl_2C_6H_3$, R^2 = Ph
i R = H, R^1 = Ph, R^2 = Ph; **j** R = H, R^1 = 2,4-$Cl_2C_6H_3$, R^2 = Ph
k R = H, R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = Ph
l R = H, R^1 = 3,4-$(OCH_2O)C_6H_3$, R^2 = Ph
m R = H, R^1 = 3,4-(OCH_2O)-6-$O_2NC_6H_2$, R^2 = Ph
n R = H, R^1 = *i*-Pr, R^2 = Ph; **o** R = H, R^1 = *s*-Bu, R^2 = Ph
p R = H, R^1 = *n*-Pr, R^2 = Ph; **q** R = H, R^1 = 4-BnO, R^2 = Ph
r R = Me, R^1 = Ph, R^2 = 4-ClC_6H_4; **s** R = 8-Me, R^1 = R^2 = 4-ClC_6H_4
t R = Me, R^1 = 3-MeC_6H_4, R^2 = 4-ClC_6H_4
u R = Cl, R^1 = Ph, R^2 = 4-ClC_6H_4; **v** R = Cl, R^1 = R^2 = 4-ClC_6H_4
w R = H, R^1 = 4-ClC_6H_4, R^2 = CO_2Et
x R = H, R^1 = 4-ClC_6H_4, R^2 = *n*-Bu
y R = H, R^1 = 4-ClC_6H_4, R^2 = $SiMe_3$
z R = H, R^1 = 4-ClC_6H_4, R^2 = 4-MeC_6H_4
aa R = H, R^1 = 4-ClC_6H_4, R^2 = 3-MeC_6H_4

Scheme 48



184a (43%) **184b** (57%) **184c** (74%) **184d** (68%) **184e** (65%)

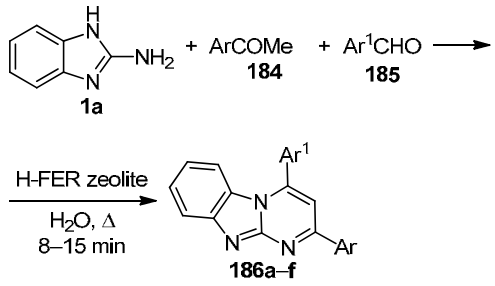
184f (67%) **184g** (72%) **184h** (72%) **184i** (65%)

184j (62%) **184k** (76%) **184l** (70%) **184m** (63%)

184n (70%) **184o** (60%)

In 2014, multicomponent condensation between acetophenones **184**, aminobenzimidazole **1a**, and aromatic aldehydes **185** was carried out by Hassaneen and Farghaly.[126] The reaction was carried out in H_2O in the presence of H-ferrierite zeolite for the short period of time of 8–15 min. The developed method made it possible to obtain a new series of pyrimido[1,2-*a*]benzimidazoles **186a–f** in good yields (Scheme 49).

Scheme 49



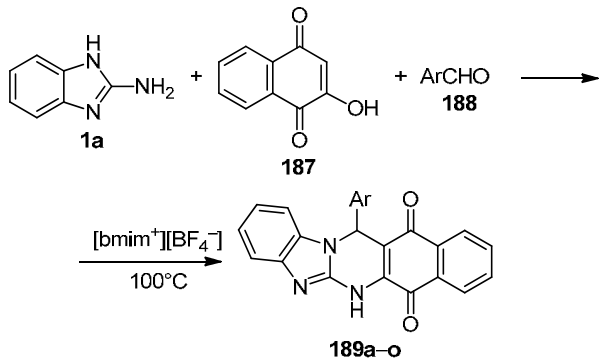
186 a Ar = Ar^1 = 4-FC_6H_4 (85%)
b Ar = 4-FC_6H_4, Ar^1 = 4-BrC_6H_4 (85%)
c Ar = 4-FC_6H_4, Ar^1 = 4-MeC_6H_4 (88%)
d Ar = 4-FC_6H_4, Ar^1 = 4-$MeOC_6H_4$ (87%)
e Ar = 3,4-$(MeO)_2C_6H_4$, Ar^1 = 4-FC_6H_4 (81%)
f Ar = 3,4,5-$(MeO)_3C_6H_4$, Ar^1 = 4-FC_6H_4(80%)

Chinese researchers have demonstrated the possibility of using 1-benzyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) as an effective catalyst in the three-component condensation of aminobenzimidazole **1a**, 1,4-naphthoquinone (**187**), and aromatic aldehydes **188** for the synthesis of derivatives of pyrimido[1,2-*a*]benzimidazoles **189a–o** (Scheme 50).[127] When selecting the conditions, it was found that carrying out the reaction in the absence of a solvent at 100°C allows one to achieve better yields (Table 6).

Table 6. The yields of pyrimido[1,2-*a*]benzimidazole derivatives **89a–o**

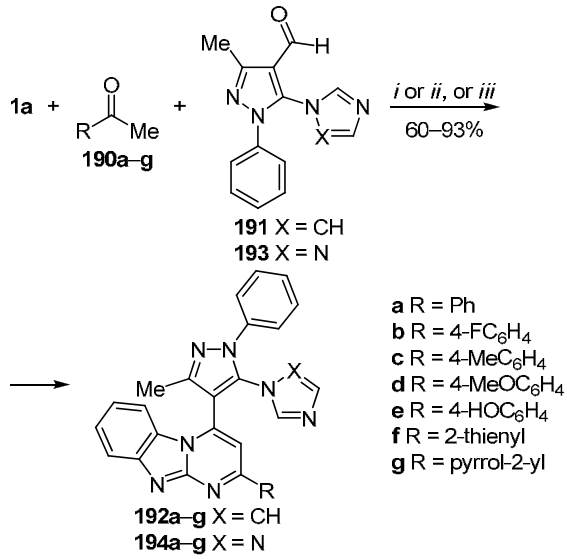
Compound	R	Reaction time, min	Yield, %
189a	4-ClC_6H_4	11	83
189b	3-FC_6H_4	11	83
189c	3-HOC_6H_4	12	85
189d	4-FC_6H_4	12	86
189e	3-ClC_6H_4	11	86
189f	3-ClC_6H_4	12	86
189g	2,3-$Cl_2C_6H_3$	12	85
189h	4-BrC_6H_4	12	85
189i	2-BrC_6H_4	12	84
189j	2-ClC_6H_4	14	82
189k	3,4-$(MeO)_2C_6H_3$	11	86
189l	2-$MeOC_6H_4$	12	84
189m	3,4-$Cl_2C_6H_3$	14	83
189n	2,3-$(MeO)_2C_6H_3$	13	85
189o	2,4-$Cl_2C_6H_3$	14	86

Scheme 50



As mentioned earlier, microwave irradiation in most cases has a positive effect on the course of a MCR. Thus, in one of the studies, microwave irradiation was used for the three-component condensation of benzimidazole **1a**, ketone derivatives **190**, and aldehydes **191**, **193** to obtain pyrimido-[1,2-*a*]benzimidazole derivatives (Scheme 51). The yields of compounds **192a–g** ranged from 60 to 93%, the yields of compounds **194a–g** – from 67 to 92%.[128]

Scheme 51

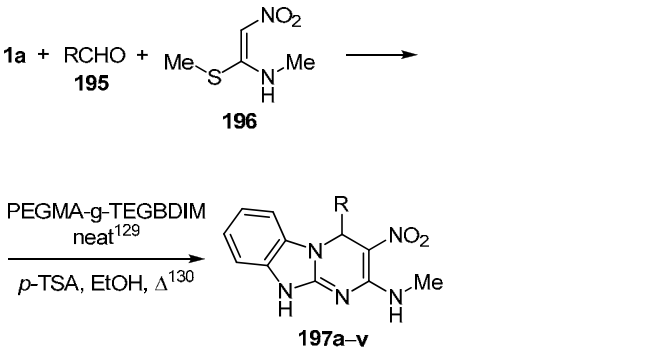


i (X = CH): KOH, EtOH, H_2O, MW (340 W), 15–20 min
ii (X = N): 1. KOH, EtOH, H_2O, rt, 10 min;
2. MW (340 W), 10–15 min
iii (X = N): 1. KOH, EtOH, H_2O, rt, 10 min; 2. Δ, 28 h

In another example of constructing the pyrimido[1,2-*a*]-benzimidazole structure under the MCR conditions, 2-aminobenzimidazole (**1a**), aromatic aldehydes **195**, and (*E*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethylenamine (**196**) were used as the reaction components.[129,130] The process was carried out by melting the components in the presence of a novel ionic liquid based on imidazolium dication grafted onto a polyethylene glycol methacrylate support PEGMA-g-TEGBDIM,[129] or by heating in EtOH under reflux in the presence of PTSA as a catalyst (Scheme 52).[130]

A characteristic of the described approach lies in the possibility of accessing nitro derivatives of pyrimido-

Scheme 52



a R = 4-ClC_6H_4 (91%), **b** R = 4-BrC_6H_4 (89%),
c R = 2-ClC_6H_4 (89%), **d** R = 3-FC_6H_4 (87%), **e** R = 4-FC_6H_4 (90%),
f R = 3-$MeOC_6H_4$ (91%), **g** R = 4-$MeOC_6H_4$ (91%),
h R = 3,4,5-$(MeO)_3C_6H_2$ (90%), **i** R = 1-Naphth (87%),
j R = Ph (91%), **k** R = 3-$O_2NC_6H_4$ (88%), **l** R = 2-BrC_6H_4 (89%),
m R = 3-BrC_6H_4 (88%), **n** R = 2-F-5-BrC_6H_3 (90%),
o R = 2-thienyl (90%), **p** R = 2-Fur (91%), **q** R = 4-Py (89%),
r R = 4-HOC_6H_4 (90%), **s** R = 4-MeC_6H_4 (91%),
t R = 2-MeC_6H_4 (89%), **u** R = 3-ClC_6H_4 (88%),
v R = 2-Cl-5-FC_6H_3 (90%)

benzimidazoles **197a**–**v**. It is known that nitroazolopyrimidines and their derivatives possess useful biological activity.[33,131–135] In addition, the presence of such an important structural fragment as the nitro group seems to be promising from the point of view of further transformations, for example, in the creation of polycyclic purine-like structures.[136]

Biological activity of pyrimidobenzimidazole derivatives

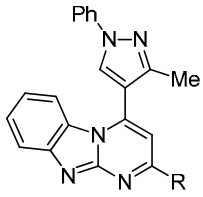
Some examples of biologically active derivatives of pyrimidobenzimidazoles are presented below. Compounds **7a**,**b** were tested for antimicrobial and antifungal activity *in vitro* against two fungal species, namely *Aspergillus niger* and *Syncephalastrum racemosum*, and four bacterial species: Gram-positive *Staphylococcus aureus*, *Enterococcus faecalis* and Gram-negative *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Table 7). Compounds **7a**,**b** did not show antifungal activity. The antimicrobial activity of these compounds was found to be lower than that of the reference drugs.

Table 7. Antimicrobial activity of compounds **7a**,**b***

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	*Enterococcus faecalis*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
7a	17.3 ± 0.63	NA**	17.4 ± 0.58	NA
7b	19.3 ± 1.2	NA	19.2 ± 0.58	NA
Ampicillin	23.8 ± 1.2	27.4 ± 0.72	NA	NA
Ciprofloxacin	NA	NA	25.3 ± 1.2	23.4 ± 0.63

* Activity is expressed as the diameter of the zone of inhibition (mean ± standard deviation), mm.
** NA – no activity.

Table 8. *In vitro* antibacterial activity of compounds **9a**–**d***



9a R = Ph
b R = 4-ClC_6H_4
c R = 2-thienyl
d R = 4-(1,3-diphenylpyrazolyl)

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
9a	16.7 ± 0.3	16.4 ± 0.3	10.4 ± 0.3	8.1 ± 0.3
9b	18.5 ± 0.3	13.7 ± 0.3	9.4 ± 0.3	6.8 ± 0.3
9c	18.5 ± 0.5	20.4 ± 0.6	15.5 ± 0.3	18.4 ± 0.2
9d	24.1 ± 0.3	20.2 ± 0.4	19.0 ± 0.3	20.3 ± 0.3
Penicillin G	26.2 ± 0.3	24.6 ± 0.3	–	–
Streptomycin	–	–	26.7 ± 0.5	20.6 ± 0.8

* Activity is expressed as the diameter of the zone of inhibition (mean ± standard deviation), mm.

Pyrimidobenzimidazoles **9a**–**d** were tested for antibacterial activity against Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* (Table 8).[39]

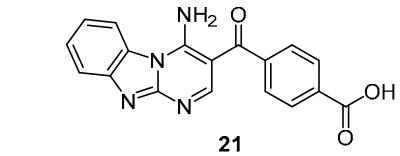
As seen in Table 8, compound **9d** showed the best activity against both Gram-positive and Gram-negative bacteria: its values of the zones of inhibition are close to those of the reference drugs.

The study of the biological activity of pyrimidobenzimidazole structures **21**, **23** was presented in a study from 2017.[45] *In vitro* antiproliferative activity of these compounds against the MCF-7 cell line was investigated. While compound **23** showed good activity, benzoic acid derivative **21** was found to be inactive (IC_{50} values 18.2 and 41 μg/ml, respectively). Antimicrobial activity of compounds **21** and **23** against Gram-positive bacteria *Bacillus subtilis*, *Streptococcus pneumoniae* and Gram-negative bacteria *Pseudomonas aeruginos* and *Escherichia coli* was investigated. Compared with the reference drug amphotericin B, compounds **21** and **23** exhibited moderate activity (Table 9).

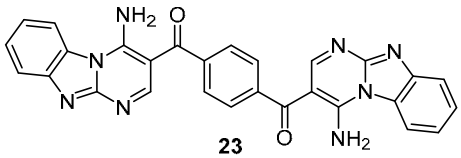
In vitro studies of a wide range of pyrimido[1,2-*a*]-benzimidazoles **55a**–**k** for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Vibrio parahaemolyticus*, and *Proteus mirabilis* were presented using chloramphenicol as a standard antibacterial agent with a broad spectrum of action. Based on the results of the *in vitro* studies, compounds **55a**,**c** were selected as candidates for further biological tests (Table 10).[57]

The synthesized galeterone derivatives containing a pyrimidobenzimidazole fragment were tested for anti-proliferative activity. The values of the maximum inhibition

Table 9. Antimicrobial activity of compounds **21** and **23***



21

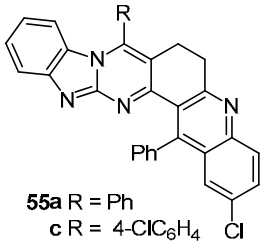


23

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Streptococcus pneumoniae*	*Pseudomonas aeruginosa*	*Escherichia coli*
21	18.7 ± 0.25	16.2 ± 0.58	–	17.3 ± 0.44
23	16.2 ± 0.44	13.9 ± 0.19	–	15.8 ± 0.19
Amphotericin B	25.4 ± 0.1	28.7 ± 0.2	19.7 ± 0.2	23.7 ± 0.1

* Activity is expressed as the diameter of the zone of inhibition (mean ± standard deviation), mm.

Table 10. *In vitro* antibacterial activity of compounds **55a**,**c**



55a R = Ph
c R = 4-ClC$_6$H$_4$

Compound	MIC, μg/ml			
	Staphylococcus aureus	*Bacillus subtilis*	*Vibrio parahaemolyticus*	*Proteus mirabilis*
55a	95.5	55.5	10.0	110.5
55c	73.5	32.5	8.5	85.5
Chloramphenicol	3.21	1.71	3.01	2.12

of cell proliferation (GI_{50}) of compounds **60a–c**, **60'c**, **61a–c**, and **60''a** lie in the middle micromolar range (Table 11).[60]

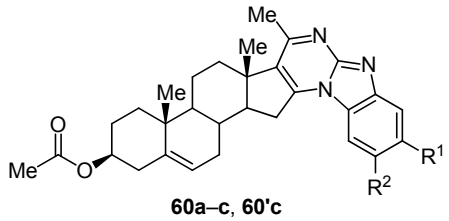
Pyrimidobenzimidazole derivatives **70**, **71 a–h**[65] showed antibacterial activity with a MIC of 2 μg/ml against Gram-positive bacteria and 1 μg/ml against Gram-negative bacteria. Compounds **70**, **71 a–h** showed antibacterial activity superior to ciprofloxacin against *Enterococcus faecalis* with a MIC of 0.2 to 0.8 μg/ml.

The antifungal activity of these compounds was evaluated in comparison with flucanozole (MIC 16 μg/ml for *Candida albicans* and 8 μg/ml for *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Fusarium oxysporum*, and *Penicillium chrysogenum*). Compounds **70f**,**g** were highly active against *Aspergillus fumigatus* and *Aspergillus flavus* with a MIC of 0.2 μg/ml. Compounds **70b**,**d**,**e**,**g**,**h** showed excellent activity against *Fusarium oxysporum* with a MIC of 0.2 μg/ml.

Cytotoxicity, expressed as percentage (%) of dead cells at a concentration of a test compound of 100 μg/ml, was assessed in comparison with 5-fluorouracil (88% dead cells) on Dalton's Lymphoma Ascites cells. Compounds **70b**,**d**,**f**,**g** and **71b**,**d**,**e**,**g** were highly active (>70% dead cells) against these cells.

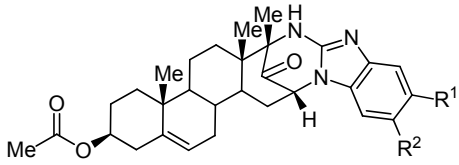
Compounds **76–79** were tested for antimicrobial and antifungal activity.[66] Compound **77** exhibited the broadest

Table 11. Antiproliferative activity of compounds **60**, **60'**, **61**, **61'**, and **60''a**



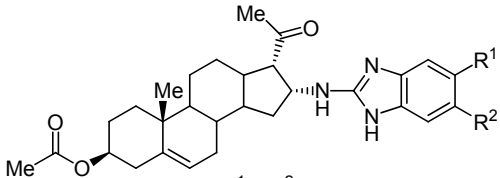
60a–c, **60'c**

	R^1	R^2
60a	H	H
60b	Me	Me
60c	H	Cl
60'c	Cl	H



61a–c, **61'c**

	R^1	R^2
61a	H	H
61b	Me	Me
61c	H	Cl
61'c	Cl	H



60''a $R^1 = R^2 = H$

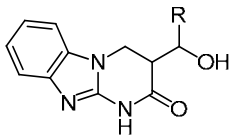
Compound	GI_{50}, μM			
	22Rv1-ARE14*	C4-2*	VcaP*	PC3**
60a	7.2 ± 1.5	22.5 ± 2.3	>50	>50
60b	40.0 ± 10.0	36.5 ± 0.2	>50	>50
60c	29.9 ± 3.1	24.4 ± 1.6	>50	>50
60'c	>50	>50	>50	>50
60d	26.3 ± 3.7	>50	>50	>50
60e	12.4 ± 5.1	12.7 ± 0.5	20.7 ± 0.9	7.8 ± 0.7
60f	1.4 ± 0.72	1.7 ± 0.4	2.0 ± 0.3	>100
60g	>50	>50	>50	>50
60h	4.3 ± 3.7	1.1 ± 0.1	>50	>50
61a	5.4 ± 0.3	18.0 ± 2.1	>50	>50
61b	7.4 ± 0.6	>50	n. t.*[4]	>50
61c	>50	>50	n. t.*[4]	>50
60''a	6.2 ± 0.7	11.9 ± 0.1	20.3 ± 1.6	29.5 ± 7.8
Galeterone***	37.8 ± 0.7	>40 (74.3%)	>40 (57.2%)	37.7 ± 1.7
Enzalutamide	>40 (84.0%)	>40 (91.5%)	>40 (61.2%)	>40 (74.0%)

* Androgen receptor positive cell lines.
** Androgen receptor negative cell line.
*** Data in parentheses represent viability in the presence of 40 μM concentration of compound.
*[4] Not tested.

spectrum of antimicrobial activity. All compounds exhibited antifungal activity. The best indicators for compounds **76** and **77** were against *Aspergillus flavus*; for compound **79** – against *Fusarium oxysporum*, and for compound **78** – against *Aspergillus ochraceus*.

Pyrimidobenzimidazoles **129** were evaluated for pesticidal activity.[75] Derivatives **129a–d** were the most active against *Plutella xylostella* at a concentration of 100 mg/ml with a lethality of 70–90%. At a concentration of compounds **129a–d** of 500 mg/ml, the lethality against *Tetranychus cinnabarinus* was 100% (Table 12).

Table 12. Toxicity of compounds **129a–d** against *Tetranychus cinnabarinus* and *Plutella xylostella*



129a–d

Compound	R	Lethality, %	
		*Tetranychus cinnabarinus**	*Plutella xylostella***
129a	4-ClC_6H_4	100	80
129b	4-FC_6H_4	100	70
129c	4-$O_2NC_6H_4$	100	90
129d	2-Fur	100	80

* Concentration of compounds **129a–d** 500 mg/ml.
** Concentration of compounds **129a–d** 100 mg/ml.

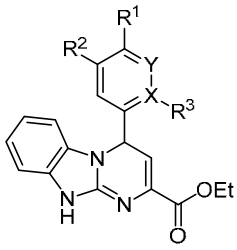
For structures **133a–e**,**g–j**, an *in vitro* study of inhibition of acetylcholinesterase was carried out. The results in comparison with known inhibitors are presented (Table 13).[78] Compounds **133d**,**e** showed the best result among other compounds **133** and significantly higher inhibitory efficacy at lower IC_{50} values in comparison with drugs tacrine and galantamine.

Compound **135** was studied against Gram-positive, Gram-negative bacteria, as well as against the fungi *Geotrichum candidum* and *Aspergillus fumigatus*[79] (Table 14). Compound **135** exhibited both antimicrobial and antifungal activity, but showed MIC values much higher than those of the reference drugs.

Pyrimidobenzimidazole derivatives **137a–g** were evaluated *in vitro* for antioxidant activity[80] (Table 15). The evaluation was carried out in two directions: a) interaction with DPPH (1,1-diphenyl-2-picrylhydrazyl) and b) inhibition of sodium linoleate peroxidation by 2,2'-azobis-(2-amidinopropane) dihydrochloride (AAPH) and soy lipoxygenase (LOX). Such well-known antioxidant agents as nordihydroguaiaretic acid (NDGA), ionol (BHT), and trolox were selected as objects of comparison. According to the results of the study, the most effective compound with antioxidant activity against peroxidation was compound **137a**, while derivatives **137d**,**e** showed moderate activity.

The affinity for human adenosine receptors A1, A2A, A2B, and A3, expressed in transfected HeLa (hA2A) and

Table 13. The profile of acetylcholinesterase inhibition *in vitro* by compounds **133a–e**,**g–j**

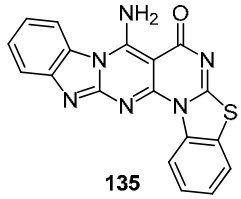


a $R^1 = R^2 = R^3 = H$, Y = CH, X = C
b $R^1 = Br$, $R^2 = R^3 = H$, Y = CH, X = C
c $R^1 = Me$, $R^2 = R^3 = H$, Y = CH, X = C
d $R^1 = H$, $R^2 = Br$, $R^3 = F$, Y = CH, X = C
e $R^1 = Br$, $R^2 = H$, $R^3 = Cl$, Y = CH, X = C
g $R^1 = H$, $R^2 = Br$, $R^3 = F$, Y = N, X = C
h $R^1 = OH$, $R^2 = R^3 = H$, Y = CH, X = C
i $R^1 = R^2 = H$, $R^3 = F$, Y = CH, X = C
j $R^1 = R^2 = H$, $R^3 = NO_2$, Y = CH, X = C

133a–e,**g–j**

Compound	Inhibition (at 208 nM), %*	IC_{50}, nM
133a	53	70.78 ± 10.01
133b	70	52.64 ± 1.07
133c	62	91.8 ± 3.6
133d	**76**	**46.86 ± 1.16**
133e	**74**	**42.52 ± 5.17**
133g	69	71.48 ± 5.04
133h	61	67.32 ± 4.94
133i	67	52.58 ± 15.65
133j	65	68.4 ± 7.94
Tacrine	66	551.58 ± 19.17
Galantamine	–	360 ± 101

Table 14. Antimicrobial and antifungal activity (MIC, μg/ml) of compound **135**

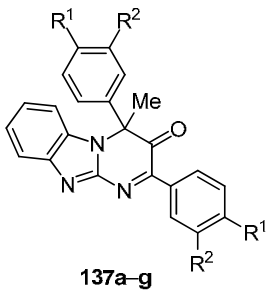


135

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Streptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeruginosa*
135	100	100	100	12.5
Streptomycin	3.125	3.125	6.25	6.25
Chloramphenicol	6.25	6.25	6.25	6.25
	Fungi			
	Geotrichum candidum		*Aspergillus fumigatus*	
135	25		50	
Triflucan	3.125		3.125	

HEK-293 (hA2B) cells for compounds **178a–h** was studied *in vitro* (Table 16).[120] Along with tricyclic compounds, monocyclic 3,4-dihydropyridin-2(1*H*)-ones, bicyclic pyrrolopyrimidinones, and furopyrimidinediones were also considered. Pyrimidobenzimidazoles, in particular compounds **178a–d**,**g**,**h**, showed the best affinity for the hA_{2B} receptor ($K_i \leq 25$ nM). The selective A_1 receptor antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) and the selective A_{2A} receptor antagonist ZM241385 were used as reference drugs.

Table 15. Antioxidant activity of compounds **137a**–**g** assessed by the interaction with DPPH and *in vitro* inhibition of sodium linoleate peroxidation by APPH and LOX, and the lipophilicity index (*C* log*P*)



137a–g

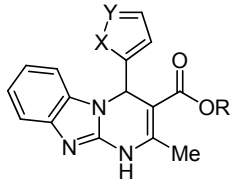
	R^1	R^2
137a	H	H
137b	Me	H
137c	H	Me
137d	OMe	H
137e	H	OMe
137f	Br	H
137g	H	Br

Compound	*C* log*P*	Antioxidant activity, %					
		DPPH (0.05 mM)		AAPH		LOX	
		20 min	60 min	0.01 mM	0.1 mM	0.01 mM	0.1 mM
137a	5.03	2	1	11	100	49	100
137b	6.03	–	–	8	80	–	40
137c	6.03	4	5	35	84	–	19
137d	4.87	3	2	3	100	–	–
137e	6.45	2	2	33	97	–	–
137f	6.75	3	2	9	78	51	61
137g	6.56	–	3	51	88	–	12
NDGA	3.92	81	83	–	–	40	84
BHT	5.43	31	60	–	–	–	–
Trolox	3.09	–	–	–	63	–	–

A team of scientists from India synthesized pyrimidobenzimidazole derivatives **192**, **194 a**–**g** and studied *in vitro* their antimicrobial, anti-tuberculosis (Table 17), and antimalarial activity (Table 18).[128] Most of the compounds tested for antimicrobial activity showed excellent potential in relation to *Salmonella typhi*, *Streptococcus pneumoniae*, *Bacillus subtilis*, and *Clostridium tetani* compared to the antibiotic ampicillin. Compounds **192c**,**g** and **194f**,**g** (MIC 100 μg/ml) exhibited activity greater than ampicillin (MIC 250 μg/ml) and equal to ciprofloxacin (MIC 100 μg/ml).

According to *in vitro* antifungal screening data, compound **194b** exhibited activity against *Candida albicans* (MIC 100 μg/l), equivalent to nystatin, while compound **192f** turned out to be also highly active (MIC 250 μg/ml), surpassing the known drug griseofulvin (MIC 500 μg/ml). The activity of compounds **192b**,**d**,**e** and **194b**,**e**,**f** against *Trichophyton rubrum* was equal to nystatin and griseofulvin (MIC 500 μg/ml).

Table 16. Affinity of pyrimidobenzimidazoles **178a**–**h** for human adenosine receptors



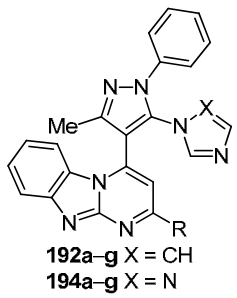
178a–h

a R = Et, X = O, Y = CH
b R = *i*-Pr, X = O, Y = CH
c R = Et, X = CH, Y = O
d R = *i*-Pr, X = O, Y = CH
e R = Et, X = S, Y = CH
f R = *i*-Pr, X = S, Y = CH
g R = Et, X = CH, Y = S
h R = *i*-Pr, X = CH, Y = S

Compound	K_i, nM, or inhibition, %*			
	hA_1	hA_{2A}	hA_{2B}	hA_3
178a	5%	14%	12.03 ± 0.7	1%
178b	20%	25%	3.49 ± 0.2	2%
178c	7%	11%	20.60 ± 1.1	1%
178d	12%	22%	11.40 ± 0.5	2%
178e	8%	16%	484.6 ± 3	1%
178f	1%	17%	371.2 ± 5	3%
178g	3%	10%	29.71 ± 1.2	2%
178h	11%	3%	29.34 ± 1.1	21%
[^{3}H] DPCPX**	2.20 ± 0.2	157 ± 2.9	73.24 ± 1.4	1722 ± 11
[^{3}H] ZM241385**	683 ± 4.1	1.9 ± 0.1	65.7 ± 1.1	863 ± 4.0

* Data are expressed as K_i or percent inhibition of specific binding at 1 μM concentration of compound (n = 2) for those compounds that did not completely displace radioligand binding.
** [^{3}H]DPCPX and [^{3}H]ZM241385 were used as radioligands in binding assays.

Table 17. *In vitro* anti-tuberculosis activity of compounds **192**, **194 a**–**g** against *Mycobacterium tuberculosis* H37Rv at a concentration of 250 μg/ml



192a–g X = CH
194a–g X = N

a R = Ph
b R = 4-FC_6H_4
c R = 4-MeC_6H_4
d R = 4-$MeOC_6H_4$
e R = 4-HOC_6H_4
f R = 2-thienyl
g R = pyrrol-2-yl

Compound	Inhibition, %	Compound	Inhibition, %
192a	61	**194b**	94
192b	91	**194c**	62
192c	78	**194d**	85
192d	64	**194e**	90
192e	83	**194f**	74
192f	65	**194g**	73
192g	61	Rifampicin	98
194a	70	Isoniazid	99

Table 18. *In vitro* antimalarial activity of compounds **192**, **194 a**–**g** against *Plasmodium falciparum*

Compound	IC_{50}, μg/ml	Compound	IC_{50}, μg/ml
192a	0.051	**194b**	0.041
192b	0.030	**194c**	1.50
192c	1.84	**194d**	1.45
192d	1.52	**194e**	0.054
192e	1.19	**194f**	0.83
192f	1,75	**194g**	0.092
192g	0.079	Chloroquine	0.020
194a	1.45	Quinine	0.268

When screening for anti-tuberculosis activity, it was found that compounds **192b** and **194b**,**e** have the highest efficacy with an inhibition rate of 91, 94, and 90%, respectively. The rest of the compounds showed weak inhibition of the growth of *Mycobacterium tuberculosis*.

Compounds **192a**,**g** and **194b**,**e**,**g** showed the best activity against the *Plasmodium falciparum* strain with IC_{50} values in the range of 0.030–0.092 μg/ml (Table 18). The authors identify compounds **192b** and **194b**,**e** as promising antimicrobial, anti-tuberculosis, and antimalarial agents.

This review systematizes the results on the creation of pyrimidobenzimidazole structures over the past 10 years. The obtained compounds demonstrate a wide spectrum of biological activity, comparable to the activity of existing drugs on the market. Thus, pyrimidobenzimidazoles are promising objects in the search for means of combating diseases on a global scale and deserve the most serious attention in further studies of their structural modifications.

The reported study was funded the RFBR, project No. 19-33-90161.

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